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December 2016

Study on the economic impact of the Paediatric Regulation, including its rewards and incentives

Final Report, SANTE/2015/D5/023

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(Redacted version)

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December 2016

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The current study is aimed at providing a review of the economic impacts of the Regulation since it entered into force until the end of 2015. This study thus covers the following dimensions: (i) Analysis of the regulatory costs to the pharmaceutical industry for meeting legal obligations; (ii) Analysis of the economic value of the rewards/ incentives to the pharmaceutical industry; (iii) Overall assessment of the rewards/ incentives to the pharmaceutical industry; (iv) Analysis of the direct and indirect social and economic benefits; and (v) Exploratory high-level cost-benefit assessment providing estimates of the broad economic impacts. The regulatory costs analysis is based on data provided by PIP and waiver applicants by means of a survey questionnaire and follow-up interviews. The analysis of the economic value of the rewards and incentives is based on data available from IMS Health. A consultation on the societal benefits of the Regulation was conducted through a two-stage survey to expert stakeholders. The economic model developed here explores the cost-benefit profile for eight medicinal products in detail, while extrapolates in relation to 108 additional PIPs that have already received a positive statement of compliance. Spillover effects of the R&D investment are also considered.

Français

L'étude en cours vise à fournir un examen des incidences économiques du règlement depuis son entrée en vigueur jusqu'à la fin de 2015. Cette étude couvre les dimensions suivantes : (i) Analyse des coûts réglementaires de l'industrie pharmaceutique pour le respect des obligations légales ; (ii) Analyse de la valeur économique des récompenses et incitations à l'industrie pharmaceutique ; (iii) Évaluation globale des récompenses et incitations à l'industrie pharmaceutique ; (iv) Analyse des avantages sociétaux et économiques directs et indirects ; et (v) Analyse coût-bénéfice exploratoire de haut niveau fournissant des estimations sur les impacts économiques généraux. L'analyse des coûts réglementaires était basées sur une consultation des demandeurs de PIP et de dérogation au moyen d'un questionnaire d'enquête ainsi que d'entrevues de suivi. L'analyse de la valeur économique des récompenses et incitations était basée sur les données disponibles d'IMS Health. Une consultation sur les impacts sociétaux du Règlement a été menée à l'aide d'une enquête en deux étapes auprès des parties prenantes. Le modèle économique développé ici explore le profil coût-bénéfice pour huit médicaments en détail, alors qu'il extrapole par rapport à 108 PIPs supplémentaires qui ont déjà reçu un avis positif de conformité. Les effets de retombée ('spillover') de l'investissement en R & D sont également pris en compte.

Executive summary

The Paediatric Regulation was enacted in the European Union in 2007 to encourage development of suitable medicine for children, promote high quality research, improve the information available on the use of medicines in children, and to prioritise the therapeutic needs in this group.

The current study is aimed at providing a review of the economic impacts of the Regulation since it entered into force until the end of 2015. This study covers the following dimensions:

- Analysis of the regulatory costs to the pharmaceutical industry for meeting legal obligations
- Analysis of the economic value of the rewards/ incentives to the pharmaceutical industry
- Overall assessment of the rewards/ incentives to the pharmaceutical industry
- Analysis of the direct and indirect social and economic benefits
- Exploratory high-level cost-benefit assessment providing estimates of the broad economic impacts

The regulatory costs analysis aimed to capture and assess all the costs incurred by the sponsors of paediatric clinical trials within the scope of Paediatric Investigation Plans (PIPs). Cost estimates were based on a consultation of PIP and waiver applicants by means of a survey questionnaire and follow-up interviews. The total cost of the Paediatric Regulation incurred to industry is estimated to be €2,106m per year or €16,848m for the years 2008-2015. The annual cost estimate includes €2,103m PIP-related compliance costs and €3.6m costs for waiver applications. On average, the estimated costs made in relation to in-vitro studies and animal studies and the development of a paediatric formulation are relatively lower than the costs of Phase II and Phase III paediatric clinical trials, and some of the other R&D costs incurred in relation to the PIP, such as pharmacokinetics and pharmacodynamics studies. The variation in cost is also dependent on the number of modifications to the PIP, the number of clinical studies, the number of paediatric subjects, the duration of the PIP, and therapeutic area.

The analysis of the economic value of the rewards and incentives provided under the Paediatric Regulation - in relation to the six-month SPC extension (article 36), the Orphan reward (article 37) and the PUMA reward (article 38) - is based on a methodological framework that considers the additional period of protection (from competition with generic medicines) that is awarded to originator companies. Moreover, because the introduction of generic medicines is delayed, society does not benefit from increased competition and lower prices for the duration of the exclusivity extension and this effect is also accounted for in the framework.

The analysis on SPC extensions covers 8 medicinal products which received SPC extensions in the period between 2007-2012 and lost their exclusivity before the third quarter of 2014. The analysis, based on data available from IMS Health, shows that there are significant differences between products and countries. The data analysis shows that the price drop of branded products often starts in the first quarter after the loss of exclusivity, this price drop is often limited in scale (up to 10-20%). During the first and second year after the loss of

exclusivity, the branded prices decrease further, and there are significant differences between products and countries. In stabilised market situations, the economic value as a percentage of 6-month revenue varies between 11% and 94%. The combined economic value (or monopoly rent) of the 8 products is calculated to amount to €517m. The economic value was then extrapolated in order to assess the magnitude of the 'full' economic value of the reward up to December 2015. This includes an extrapolation of the economic value of the products studied in detail to countries where SPC extension was granted but our datasets did not include those geographies. In addition, the economic value of a further four products (with SPC extension ending within the research period) was estimated based on the average economic value per capita. The extrapolated economic value thus amounts to €926m between 2007-2015.

There are four products with Orphan reward to date that may be studied but since these are still under protection it was not possible to estimate the economic value of the reward. Projection of currently available data towards the loss of exclusivity in the future is unreliable. However, the approach to estimate the economic value of Orphan rewards could, in principle, be similar to the model used for the SPC extension, with the main difference being the delay of two years rather than 6 months.

There are only two PUMAs that were authorised up to December 2015. Given the limitations of the available data, it is not possible to project the economic value of these PUMA rewards. There is however a fundamental difference with respect to estimating the SPC reward: market exclusivity period for a product starts at the moment the PUMA reward is granted instead of after a delay as for the SPC-extension. This implies that the 'economic value' covers the 'monopoly benefits' a product receives from additional data exclusivity (8 years) and market protection (2 years). A model was developed that could be applied in future studies.

An assessment of the rewards to industry is based on five specific evaluation criteria: relevance, effectiveness, efficiency, coherence, and utility/potential for improvement. We collected data through a survey to pharmaceutical companies, which was complemented with interviews and desk research. The objectives of the reward scheme are deemed highly relevant when considering that the rewards provide a way for organisations to sponsor and support the development of paediatric medicines. Nevertheless, the rewards themselves cannot guarantee capital allocation decisions that maximise value for companies or result in positive return on investment in individual R&D programmes.

The Regulation and hence the combination of obligations and rewards is seen as effective to shift focus to paediatric medicine development. As a result, the amount and quality of research and information available for the paediatric population has already increased. Over the period between 2007-2015, the share of paediatric trials among all clinical trials increased 2.5-fold and over 100 PIPs were completed. Paediatric clinical research networks have been set up involving academia and industry. Industry also changed their approach to medicine development and now design their research and development plans incorporating the paediatric population. The Regulation is considered as a commendable first step in the right direction but there remain therapeutic areas where significant unmet need continues to exist, such as in the field of paediatric oncology, and hence further steps and more time is needed to achieve the expected impact. It is claimed that therapeutic areas covered by research in children is driven mainly by commercial interest and reflecting the needs of the adults rather than those of children.

It is noted that the effectiveness of the rewards is higher for high-volume products and lower for indications with very limited patient numbers. Factors influencing effectiveness include uncertainty (and discontinuity) in early product development, difficulty in recruitment of paediatric subjects, compliance check procedures, and the time-limited nature and complexity of obtaining the reward across member states once the clinical research is completed.

The extent to which rewards were taken up by companies indicate that the 6-month SPC extension is the main tool to incentivise and reward paediatric medicine development. The effectiveness of the orphan and the PUMA rewards are not immediately obvious with very few examples in the period 2007-2015. External factors, such as the continued off-label use of cheaper and comparable medicinal products represents a disincentive for paediatric medicine development. The lack of meaningful market exclusivity and unpredictable return on investment (due to pricing and reimbursement practices) in a niche market makes it difficult for PUMA to act as a strong incentive. The development of orphan drugs targeting children is complex and costly with very small study populations. Nevertheless, stakeholders consider the orphan designation as a strong incentive and expect to see an increase in orphan rewards in the coming years. One of the drawbacks highlighted was the lack of choice for companies between the orphan designation and SPC extension if the substance is also registered for non-orphan indication.

Industrial stakeholders indicate that the PIP application and administrative procedures consume significant resources. This would be seen as unattractive for smaller companies. This is despite the fact that a more streamlined process is in place since 2014 and mandatory "key binding elements" of a PIP are defined and thus the need for minor PIP modifications are decreased. Further, engaging with the regulatory system is often found to be slow, fragmented across different committees, thus resulting in additional costs and delays in product development.

There are a number of initiatives in member states which are complementary to or extending the implementation of the Regulation. For example, priority review of paediatric data and clinical trial applications in member states aimed to provide accelerated access to paediatric medicinal products. In addition, national legislation is available in some cases to reduce the off-label use of medicines for children or to use financial incentives to encourage the use of paediatric medicine. Paediatric research networks with industry/academia participation have also been created and supported at the national level. Nevertheless, there is scope for enhancing research collaboration through the mobilisation of EU research funds.

Public stakeholders indicate that the Regulation was set up from an overly narrow perspective, excluding considerations for affordability, cost-effectiveness and budget implications at the national level. From the public perspective, the effectiveness of the Regulation may be viewed as somewhat reduced because public services may ultimately decide not to pay for the registered paediatric medicines. The fact that the entry of generic medicine to market is blocked for 6 months represents a high price to pay for a branded product. Generic companies would consider important that SPC extension can only be granted to the company that sponsors a paediatric study and is responsible for the compliance with the PIP (market authorisation holder), not to other third parties.

The legislation in the US differs in various ways from the EU Regulation. The US has set up and funds the Paediatric Trials Network (enabled by the Best Pharmaceuticals for Children Act, BPCA) that, with over 100 clinical sites, conducts paediatric clinical trials and generates paediatric data on products. BPCA also provides a financial incentive (6-month market exclusivity) to companies to voluntarily conduct paediatric studies under a Pediatric Written Request (WR). These WRs are issued based on a priority list, representing a balanced portfolio of therapeutic areas and paediatric needs, without replicating research funded elsewhere. The Pediatric Research Equity Act (PREA) on the other hand is mandatory and requires an initial Paediatric Study Plan (PSP) at the end of Phase II. The EMA and FDA collaborate within the framework of the international Paediatric Cluster to exchange information, agree on scientific requirements and harmonise requests to sponsors. A current special initiative is the Pediatric Rare Disease Priority Review Voucher awarded upon approval of a new product application for rare paediatric disease indications. This is a transferable voucher for sponsors to obtain a priority review of any subsequent drug application.

A consultation on the societal benefits of the Paediatric Regulation was conducted through a two-stage survey to expert stakeholders. This survey reveals a broadly positive view of the regulation's effect on medicines development. The majority of the respondents agree or strongly agree that the number of paediatric research projects increased, that more quality information is available on approved medicines for their use in paediatric population, and that the awareness of health professionals for better evaluation of medicine for children has increased. 84% of respondents indicate that there has been a measurable increase in the numbers of medicines tested within paediatric populations in the period since the implementation of the regulation. The survey revealed a broadly positive view about improving research capacity and research collaboration, with a somewhat more neutral view expressed about any improving trends in paediatric research funding. Regarding the replacing of existing treatments for a paediatric condition (either by treatment with less toxicity or enhanced efficacy), close to half of the respondents find that the regulation had led to an increase. While 68% of the respondents find that there has been an increase in the number of children treated with the right medicine at the right time with the right dose. Almost 40% of respondents indicate they have seen improvements in child morbidity in their field, which they would attribute to the regulation, which is encouraging at this point in time. Moreover. the majority of stakeholders expect that the regulation will have measurable long-term benefits, eg improving children's school attendance, reducing time cares need to take off work to care for children, increasing quality-adjusted life years for children, and decreasing mortality rates of children with life-threatening illnesses. Positive societal benefits were also reported as part of the survey to industry, eg it was reported that the Paediatric Regulation evoked a change in culture and a significant shift in mind-set and helped encourage paediatric development become a more integral part of the overall development of medicines in Europe.

The Paediatric Regulation is expected to have a positive impact on improved treatment for children and is expected to contribute to a reduction of adverse drug reactions. This, in turn, is expected to improve the quality of life of children, avoid mortalities, hospitalisation costs, ambulatory costs, lost time by informal carers, and is expected to lead to other improvements related to better treatment for children. The (exploratory) cost-benefit analysis seeks to

contrast these benefits with the cost to society resulting from the extra monopoly rent obtained by the sponsors of PIPs as a result of the Paediatric Regulation.

There are two products (Drug A and drug B) among the eight medicinal products studied here with strongly favourable benefit-cost ratio when calculated over a 10-year period, basically due to non-cash benefits. Drug A is an Asthma pill and provides €32m net benefit, while drug B, a migraine pill provides €66m net benefit to society. All other medicinal products have a negative benefit-cost ratio over 10 years.

Based on the aggregation of cash and non-cash benefits data for eight medicinal products, it is estimated that these products yield overall benefits of €199m over a period of 10 years. Overall cash cost to society (patients, health systems) from total monopoly rent to all stakeholders (pharmaceutical industry, wholesalers, pharmacies, governments from value added/sales tax) were estimated at €590m. As a result, the overall socio-economic benefit cost ratio across these medicines is 0.34, the societal overall rate of return minus 66%. It is expected that those PIPs that have already received a positive statement of compliance but are not (yet) received a reward, on average, also have a positive effect on society resulting from the change in labelling/safer medicine. Based on an exploratory extrapolation of cost and benefits that may exist in relation to 108 of such additional PIPs, the benefit estimate arrives at around €500m, which is closer to the estimated value of monopoly rents.

The investment in R&D made in relation to the PIPs, although a cost imposed on the pharmaceutical industry, can also be viewed as an R&D investment towards new and improved medicine that triggers further investment and contributes to the creation of jobs, growth and innovative activity across (EU and non-EU) sectors. These so-called spillover effects are estimated based on rates of return that are documented in related literature. The more conservative estimated rate of return from an annual €2bn investment in R&D could, after a period of 10 years, yield a total social return of around €6bn. This estimated social return is significantly higher than the economic value of the SPC extension (excluding cost to society in relation to other products and countries, as well as the dead weight loss in relation to the SPC) suggesting that, in monetary terms, the benefits of the Paediatric Regulation outweigh the costs.

1 Introduction

This study on the economic impact of the Paediatric Regulation, including its rewards and incentives was commissioned by the European Commission DG SANTE in October 2015 (SANTE/2015/D5/023). The study was conducted by a consortium composed of Technopolis Group, Ecorys Nederland BV, and empirica GmbH between November 2015 and October 2016. In the following sections, a short historical context is provided to the study before reviewing the objectives and presenting results and conclusions.

1.1 Context of the study

The Paediatric Regulation on medicinal products for paediatric use (EC) No 1901/2006 was enacted in the European Union in 2007 to encourage the development of suitable medicine for children, promote high quality research, improve the information available on the use of medicines in children, and to prioritise the therapeutic needs in this group.[1] This is to be achieved via a set of obligations, rewards and incentives for both new/on-patent products, and off-patent products, with an additional set of tools for transparency, information and research stimulation. The Regulation also provides that those developing a medicine intended for paediatric use may request scientific advice from the European Medicines Agency (EMA). This advice is free of charge and given on the design and conduct of clinical trials required to demonstrate the quality, safety and efficacy of the medicine in the paediatric population. Applicants may request scientific advice before the preparation of a paediatric investigation plan (PIP), or to submit a PIP first and follow it up with a request for scientific advice.

The PIP should set out all proposed studies necessary to support paediatric use of the medicine, and include details of the timing and measures proposed to demonstrate quality, safety and efficacy, the three Market Authorisation criteria. It is understood that due to the nature of clinical trials with children, there would be increases in the cost and timescales of drug development following implementation of the Regulation. Complying firms are rewarded through extended exclusivity rights, SPC prolongation and extended market exclusivity.

The EMA has an expert committee, the Paediatric Committee (PDCO), including members of the Committee for Medicinal Products for Human Use (CHMP), experts from Member States, and members representing patient associations and healthcare professionals. A network of paediatric research networks (Enpr-EMA) has been created to foster collaboration within and beyond the EU and across members, patient associations, academia and the pharmaceuticals industry. The EMA is participating in regular Paediatric Cluster teleconferences with other regulatory agencies, in particular, the US Food and Drug Administration, in order to exchange information, agree on scientific requirements and harmonise requests to sponsors, leading to joint publications and common commentaries.[2]

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[1] EMA, 2013. Successes of the Paediatric Regulation after 5 years (August 2007-December 2012)

[2] See the following websites for more details:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000655.jsp&mid=WC0b01ac0580953d98 and
http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm

There are several important transparency measures, including a database of Paediatric Trials (EudraCT), a database of authorised products in the EU (EudraPharm), medicinal product information, including waivers, deferrals, compliance and corresponding results. In addition, there is an inventory of use in children by Member States, and an inventory of paediatric needs by the PDCO.

The Paediatric Regulation also stipulates (Article 50 (3)) that in 2017, the Commission shall present a report to the European Parliament and the Council on the experience acquired as a result of the application of Articles 36, 37 and 38. The report shall include an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health of this Regulation.

1.2 Objectives of the study

The current study is aimed at providing a comprehensive review of the economic impacts of the Regulation since it entered into force in January 2007 up to December 2015. The results of this economic analysis will feed into a report that the Commission is due to present to the European Parliament and the Council in 2017. Therefore, the current study will gather relevant information, provide evidence and assess the current economic impact of the Paediatric Regulation.

According to the requirements of the study, it focussed on the following four elements:

1. Quantifying and analysing the regulatory costs (administrative costs and other compliance costs) of the Paediatric Regulation, excluding the cost of enforcement and costs for public authorities;
2. Quantifying and analysing the economic value of the rewards and incentives provided under the Regulation to the pharmaceutical industry (additional monopoly rent) and evaluating its effect;
3. Quantifying and analysing the direct and indirect benefits in view of the aim of the Regulation, which is to provide better medicines for children;
4. Providing estimates regarding a high-level cost-benefit assessment from an economic perspective.

The structure of the report follows closely the above elements and presents findings in the following sections:

- Chapter 2 focuses on quantifying and analysing the regulatory costs to the pharmaceutical industry for meeting the legal obligations detailed in the Regulation; both the relevant administrative costs and other compliance costs, notably the R&D costs required to fulfil the regulatory obligations.
- Chapter 3 focuses on quantifying and analysing the economic value of the rewards/ incentives to the pharmaceutical industry provided under the Regulation and evaluating its effect.
- Chapter 4 presents an overall assessment of the rewards/ incentives to the pharmaceutical industry.

- Chapter 5 presents an analysis of the direct and indirect benefits (social and macro-economic) of the Regulation based on available published data and stakeholder perceptions.
- Chapter 6 comprises a high-level cost-benefit assessment and providing estimates of the broad economic impacts of the Regulation, considering direct costs (and potential savings) to the healthcare payer as well as tangible and intangible benefits to the society at large.
- Chapter 7 provides a summary and key conclusions of the study.

2 Regulatory costs to industry

The Regulatory costs analysis aims to capture and assess all the costs incurred by the sponsors of paediatric clinical trials within a Paediatric Investigation Plans (PIPs) or waiver applications, in particular the pharmaceutical industry, for meeting the legal obligations detailed in the Regulation for the period between 2008-2015. To the best of our knowledge, there have been no previous studies that calculated the actual costs of PIPs and waivers for the pharmaceutical industry. The objective here was to gather data directly from pharmaceutical companies across two major cost items:

- Administrative costs incurred for preparing, drafting and filing a PIP or waiver application with the EMA, annual reporting on progress with the PIP and subsequent modifications.
- Research & Development (R&D) costs of a PIP, including costs incurred in relation to preclinical studies, the development of a paediatric formulation, phase II and phase III clinical studies.

2.1 Data collection and methodology

Cost estimates are based on a consultation of PIP and waiver applicants by means of a survey questionnaire and follow-up interviews. The survey was sent to all PIP/waiver applicants that have made 3 or more PIP or waiver applications and, in addition, participants of the EU Framework Programme projects that submitted a PIP. The request to provide information on specific PIPs was thus sent to 78 companies that submitted an estimated 870 PIP/waiver applications. Note that the total number of PIP/waiver applications requested per company was capped at a maximum of 10 for practical reasons, resulting in a target sample population of 514 applications, representing 40% of the total population of 1,297 applications between 2007-2015. For additional information on survey design process and sampling frame, see Appendix A.

The cost analysis is based on data collected from 26 organisations which includes 19 companies and 7 Framework Programme participants. Company data is collected with a response rate of 24%, which is considered satisfactory due to the difficulty for companies to retrospectively collect information on specific PIP costs incurred by different teams of staff across the company and due to the confidential nature of such information. The 26 organisations that provided data voluntarily include several EFPIA member companies, one non-profit organization and six small and medium-sized companies (SMEs).

In total, data was collected on 36 waiver applications from 11 organisations (not all organisations submitted a waiver application) and on 85 PIPs from 24 organisations (two organisations only submitted waiver applications). Figure 1 presents a breakdown of the sample of PIPs according to their stage at the time of data collection. All of the PIPs had completed the initial application phase. Only four of the 85 PIPs in our sample had not yet started the R&D stage. The majority, 50 PIPs, were ongoing, 14 PIPs were discontinued and 17 PIPs had received a final compliance check. As presented in Figure 2, 11 of the PIPs in the sample correspond to medicinal product marketed in at least one EU member state. This represents a deliberate oversampling of PIPs that have received the final compliance check and/or have been put on the market. The reason for this sampling was to gain information on PIPs that have more complete data on late R&D phases. Cost information presented in the

following sections was estimated by analysing data obtained for the sample and using this data to gross up figures to characterise the entire population.

Figure 1 Distribution of PIPs with regulatory data collected, by stage

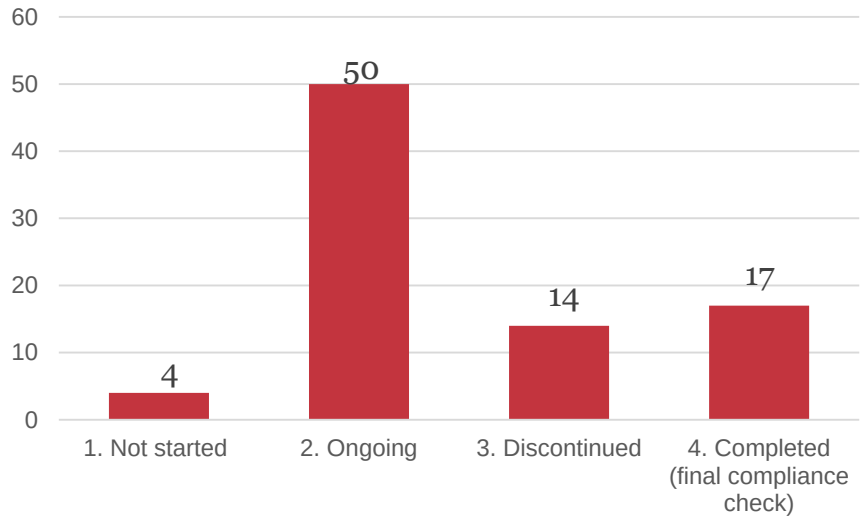
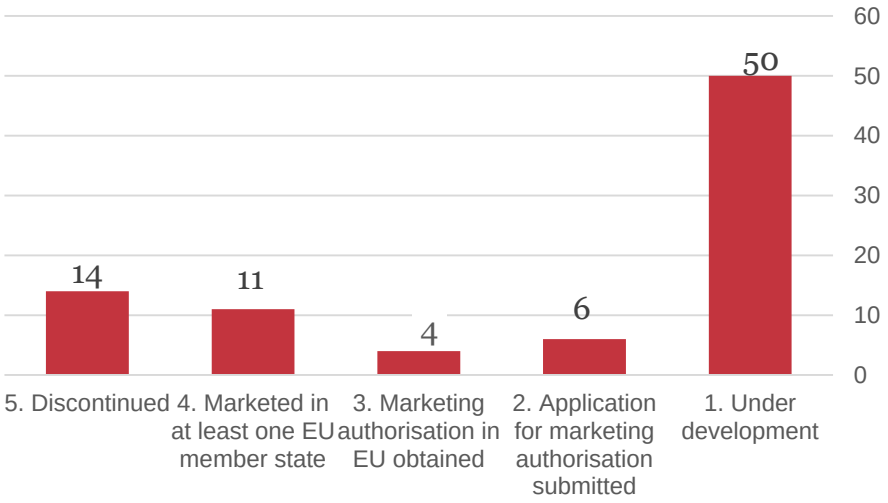


Figure 2 Distribution of PIPs with regulatory data collected, by paediatric product stage



2.2 The regulatory cost of testing medicine for the paediatric population

2.2.1 Total cost of compliance with the Paediatric Regulation

The total cost of the Paediatric Regulation incurred to industry is estimated to be €2,106m per year or €16,848m for the years between 2008-2015. This estimate includes €2,103m PIP-related compliance costs and €3.6m costs for waiver applications.

The total cost of the PIPs is estimated based on an average of 107 first PIP decisions per year for the period 2008-2015 (see Table 1). The estimated average incurred costs per PIP is, based on our sample population, €19,608k which comprises of around €728k for the

administrative costs incurred in relation to filing an initial application and for subsequent modifications of a PIP, and €18,879k for the R&D costs (4%:96%). R&D costs may include costs related to:

- In-vitro studies and animal studies
- Development of a paediatric formulation
- Phase II paediatric clinical trials - studies conducted to evaluate the efficacy and safety of the medicine
- Phase III paediatric clinical trials - studies conducted after the efficacy is demonstrated and prior to the approval of the drug
- Other R&D costs

The sample data suggests that an average of 2.9 clinical studies were agreed as part of the PIPs and this implies an average estimated cost per study of €6,831k.

Table 1 Overview of total costs of developing and executing PIPs

	Estimated annual costs
Total administrative and R&D costs of PIPs for the industry per year (2008-2015)	€2,103m
Average cost per PIP	€19,608k
Average administrative cost per PIP	€728k
Average R&D cost per PIP	€18,879k

Aggregation is based on an average of 107.3 first PIP decisions in 2008-2015 (858 first PIP decisions in 2008-2015 in total).

The total cost of the waiver application is estimated based on a calculated average number of 50.4 waiver decisions per year for the period 2008-2015 (see Table 2). The average cost of the waiver application is €70k, which is about 10% of the estimated average cost of a PIP application. The cost of waiver applications, as reported by companies, comprises of labour costs for literature searches, expert discussions, regulatory and administrative activities. Some waivers were reported to have incurred costs for additional studies (e.g. pre-clinical studies) and some waivers were not accepted in the first instance and there were subsequent costs linked to appeals. All costs reported by companies for waivers were included in the calculations.

Table 2 Overview of total costs of waiver applications

	Estimated annual costs

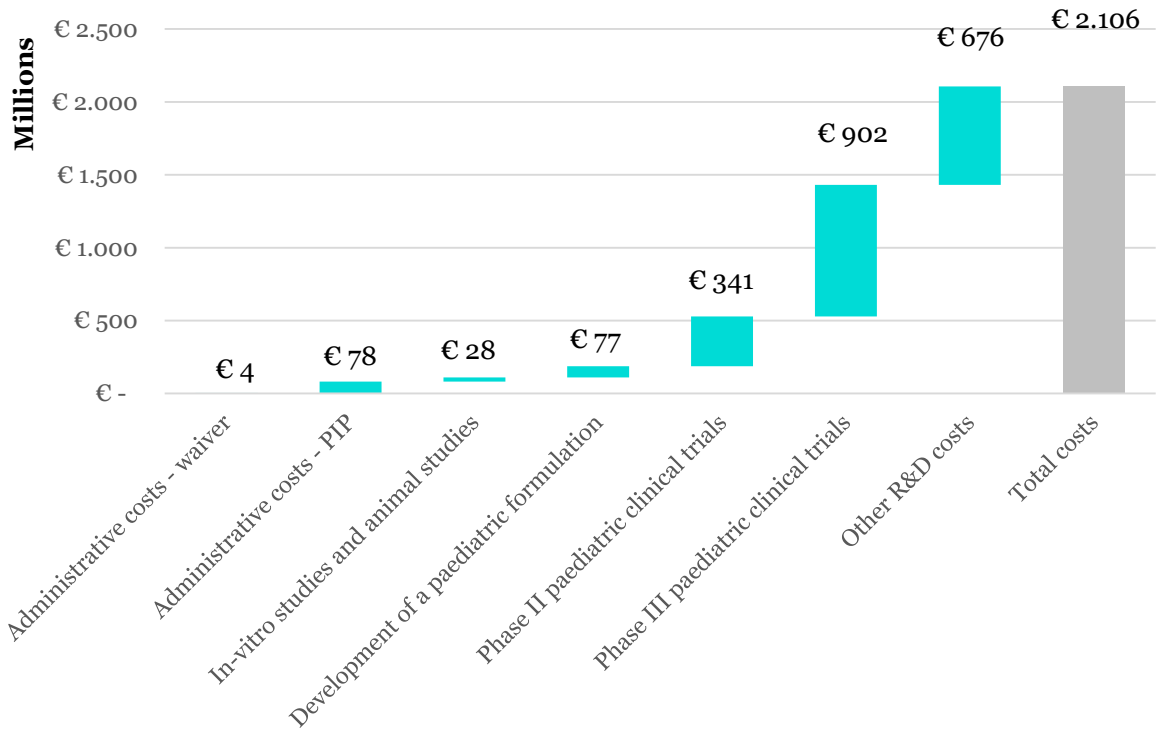
	Estimated annual costs
Total administrative costs of waiver applications for the industry per year (2008-2015)	€3,548k
Average cost per waiver application	€70k

Aggregation is based on an average of 50.4 waiver applications in 2008-2015.

2.2.2 Variation in costs by study phase

Figure 3 presents a breakdown of the total estimated costs to industry by cost category. It is clear that the R&D costs are the largest component of executing a PIP and that there is considerable variation in the estimated cost for each of the R&D phases.

Figure 3 Estimated total costs incurred in relation to the Paediatric Regulation (based on data for 2008-2015), broken down to components, per year in millions of euro



The annual administrative costs linked to PIPs are estimated to be €78m and this comprises of the preparation of the initial application, modification and reporting, and other administrative costs. The preparation of an initial application costs on average €0.4m (Table 3). Note that this average cost estimate, and the other average cost estimates presented in this section, are often incurred over multiple years. As presented in Table 3, all PIPs incur some administrative costs, even when the PIP is discontinued. Note that only 55% of the PIPs in our sample was reported to incur additional administrative costs in relation to annual reporting requirements or PIP modifications. In the event that a PIP was discontinued, 29% of the PIPs incur these additional administrative costs.

In-vitro and animal studies are estimated to cost industry €28m each year. 40% of the PIPs include such in-vitro and/or animal studies. On average, the cost of in-vitro and animal studies is €0.8m. If the PIP is discontinued, around 36% of those have already incurred this type of cost before termination.

The total development cost of paediatric formulations is estimated to be €77m per year. 47% of the PIPs incur this type of cost and 29% of the PIPs that are discontinued incur this type of cost. On average, the cost of the development of paediatric formulations, if any cost is incurred, is €1.6m.

Table 3 Estimated costs of a PIP broken down to stages (based on data for completed phases only, between 2008-2015), in millions of euro

	Average	**Median**	**Standard deviation**	**% of PIPs incurring cost**	**% of PIPs incurring cost if PIP is discontinued**
Preparation of the initial PIP application	€ 0.4	€ 0.1	0.7	100%	100%
Annual reporting and further PIP modifications	€ 0.1	<€ 0.1	0.3	55%	29%
Other administrative costs	€ 0.2	-	0.5	42%	21%
In-vitro studies and animal studies	€ 0.8	€ 0.5	0.9	40%	36%
Development of a paediatric formulation	€ 1.6	€ 0.9	1.7	47%	29%
Phase II paediatric clinical trials	€ 7.3	€ 1.7	14.3	48%	21%
Phase III paediatric clinical trials	€ 15.7	€ 1.5	22.4	72%	36%
Other R&D costs	€ 14.4	€ 1.2	22.1	44%	21%

The combined annual cost of phase II and phase III clinical trials to industry is €1,243m: €341m for phase II clinical trials and €902m for phase III clinical trials. Note again that not all PIPs include costs for a given PIP category (or stage). As indicated in Table 3, only 48% of the PIPs have incurred or are expected to incur phase II R&D trial costs and 72% have incurred or are expected to incur phase III R&D trial costs. In some cases, there may be no clear distinction between phase II and phase III costs and some survey respondents have included costs under either phase II or phase III. However, for 38% of the PIPs, data on both phase II and phase III costs is provided. On average, cost for a phase II paediatric trial is

€7.3m (median €1.7m) and average cost for a phase III paediatric trial amount to €15.7m (median €1.5m). The standard deviation of the larger cost estimates, as that for phase III paediatric clinical trials, is substantially higher – indicating that there is a high variation between costs incurred and, as expected, some of the more extreme values include very high cost estimates. As described in the next section, there are a number of factors that drive the cost of a PIP stage.

An additional estimated €676m is incurred by industry each year in relation to 'other' types of R&D costs. 44% of the PIPs for which we have collected cost data included such 'other' costs. On average, the other types of cost amount to €14.4m (median €1.2m). We are not able to fully separate the lower cost elements from the higher cost elements. However, the cost data that falls below the median [with range of approximately €7k-€1,000k] are in relation to observational studies, the preparation of study outlines, medical writing for clinical plan including data and database management, coordination activities and transaction costs, extrapolation studies and literature study to support extrapolation, other cross-functional paediatric project costs, pharmacokinetics and pharmacodynamics (PK/PD) studies, and bioavailability, modelling. Cost data that is above the median [with range of approximately €1m-€74m] are related to sponsor management costs, pharmacokinetics and pharmacodynamics (PK/PD) studies, pharmacogenomics (PGx) analysis, bioavailability, modelling and simulation studies, and costs related to supporting phase II and III trials.

2.2.2.1 Attrition

It should be noted that a considerable proportion of PIPs are discontinued and this represents costs incurred by the industry for activities that will not bring any potential reward or revenue to the company. Moreover, discontinued PIPs also place undue burden on paediatric patients involved in associated clinical trials. According to a study of PIPs in the EMA database between 2007-2010, 21% of agreed PIPs were subsequently abandoned because of discontinuation of the adult development programme for the product.[3]

The total estimated administrative and R&D costs of PIPs that are already discontinued (16% of the PIPs in our sample) amounts to €144m per year, 7% of total estimated costs. This is likely to be an underestimation of the total cost incurred in relation to discontinued PIPs because several of the PIPs that have been labelled as 'ongoing' may be discontinued at a later stage in the execution of the PIP.

Any costs associated with waiver applications, albeit much smaller, can likewise be considered as sunk costs to industry – incurred in compliance with the Paediatric Regulation.

2.2.3 Data limitations

In order to produce a cost estimate for the industry, organisations were asked to include only the fraction of their costs that was specifically related to the PIP and to exclude costs related to adult drug development from that of paediatric drug development. Many of the clinical trials however are mixed trials and organisations may have had difficulty to completely separate out costs (even though no such difficulty was reported to the study team). This means that all costs reported are considered 'incurred' to comply with the Paediatric

[3] Escher Report. Improving the EU system for the marketing authorisation of medicines: Learning from regulatory practice (2014). p 19

Regulation. Without the Paediatric Regulation, costs would not have been incurred unless an organisation would have voluntarily committed to invest in medicine development for children.

Note that incurred costs presented in this study remain cost *estimates* based on self-reporting by organisations that voluntarily engaged with the study and provided cost data input. These estimates were provided as best point estimates, however, some of these costs may be overestimations or underestimations. Based on an analysis of industries' practice of pricing drugs, e.g. for (US) Medicare recipients, Angell argues that pharmaceutical companies tend to overestimate (R&D) costs.[4]

As discussed in the next section, there are a large number of potential cost drivers, however, our survey questionnaire was not able to capture all potentially relevant cost components, and further, data supplied by organisations does not allow for a uniform coverage of all dimensions, allowing a robust analysis of every dimension. Despite these limitations, we have been able to extrapolate total cost incurred by industry using the PIP as the unit of reference (and with data obtained on both completed and incomplete phases). Nevertheless, our cost estimates remain subject to possible overestimation or underestimation, e.g. if sample data is not fully representative. In particular, our average and median cost estimates for the 'other cost' category is based on reported incurred costs, sometimes in relation to an ongoing PIP. As a result, there is potential for underestimation in this category.

The cost estimate reflects the costs industry incurred during the years 2008-2015. The cost estimate may not be an accurate reflection of costs that industry will incur in the future as a result of the Paediatric Regulation. During the years 2008-2015, on average, there were 107 decisions on initial PIP applications. Note that since 2012 onwards, the number of initial PIP decisions is stabilising at around 90 per year. This means that projected annual cost to industry, based on the current estimations, is 84% of the cost figures presented above. Similarly, there is a decreasing trend in the number of modifications per PIP and this will reduce somewhat the administrative costs of the PIP (EMA 10-year report). Likewise, organisational learning (both for industry and EMA) may contribute to more efficient/less costly PIP procedures over time.

Other cost items which represent significant costs to industry, related to providing medicine to children, but were out of scope for the current study to assess the compliance cost to industry of evaluating and developing paediatric medicine are the following:

- Cost of long-term safety and efficacy monitoring after marketing authorisation
- Legal costs of SPC extension (reward) after a positive compliance check
- Obtaining marketing authorisation for the paediatric medicine
- Marketing costs of authorised paediatric medicine
- Manufacturing and distribution costs of authorised paediatric medicine

[4] See Marcia Angell (2004). The Truth About the Drug Companies. Random House NY

2.2.4 Cost drivers

There are a number of cost drivers that influence the cost incurred in relation to a given PIP and contribute to explain the significant variations in estimated costs between PIPs.

2.2.4.1 Number of modifications to the PIP

Olski et al. (2011)[5] investigated the modifications proposed by the Paediatric Committee (PDCO) of the European Medicines Agency to the PIP applications submitted by companies from 2007 to 2009. Of the 257 PIP applications that had been submitted at the time, the PDCO requested major modifications to 38%. These requests included the development of age-appropriate formulations (11%), expansion of the scope of clinical programmes (6%), addition of a phase II/III study (17%) and the inclusion of additional age groups (13%), generally younger ones.

It is possible that engaging with the Scientific Advice Working Party (SAWP) to request free scientific advice may decrease future PIP costs. Based on our survey results, for 8% of PIPs (7 of 85) scientific advice was thought to have decreased the overall PIP costs – reduction in studies that had been initially planned or benefit of clearer development plan. However, for 7% of PIPs (6 of 85) scientific advice was thought to have increased overall PIP costs – since additional studies were suggested. Other PIPs in our sample were seen not to have benefited from scientific advice, possibly because no scientific advice was sought. According to EMA's 10-year report, there has been an increase in scientific advice sought by companies.

Nevertheless, even if a PIP has been agreed, a PIP applicant may request modifications of the PIP at a later stage, eg to reduce sample size of paediatric subjects in the clinical trial[6]. Survey respondents reported that the number of modifications to the PIP was seen as a burden and often delayed the execution of the PIP significantly (and possibly also the launch of the associated adult drug) and thus the burden and costs associated can extend beyond the administrative costs involved with requesting a modification. Despite these considerations, many PIPs have been modified once or more, however, according to EMA's 10-year report, the number of modifications is decreasing over time, possibly as a result of organisations' learning curve.

2.2.4.2 Number of clinical studies

The number of clinical studies that are part of a PIP differ considerably across the PIPs sampled. Based on the survey data, the average number of clinical studies that are agreed upon is 2.9. This is slightly higher than the average number of exclusively paediatric trials per PIP which is 2.4 (Draft 10-year report, EMA/EudraCT). However, only around 18% of the PIPs in our sample involved 3 clinical studies. Just over half of the PIPs involved only one or two clinical studies. Two of the PIPs in the sample did not involve a clinical study (only e.g. a

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[5] Olski, T.M. et al., 2011. Three years of paediatric regulation in the European Union. European Journal of Clinical Pharmacology, 67(3), pp.245–252.

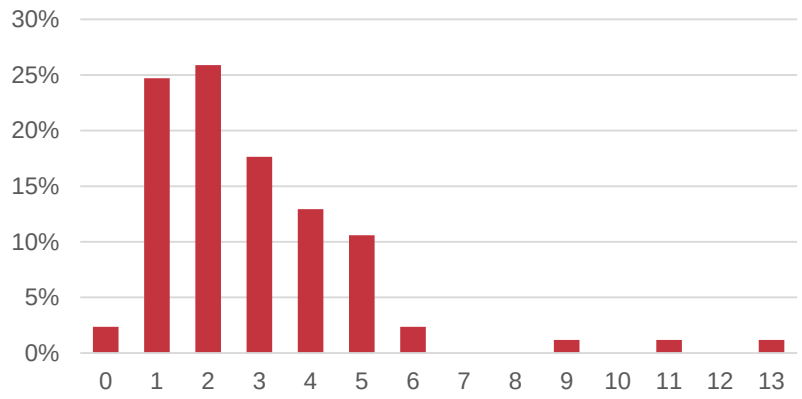
[6] Article 22 of the Regulation states: "If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee."

literature review). The highest number of clinical studies that was reported as part of a PIP is 13 (see Figure 4).

Note that there is considerable variation in cost between the different R&D stages, ie phase II and phase III are considerably more expensive than in-vitro/animal studies and the development of a paediatric formulation. However, in our sample, not all PIPs incurred costs (or expecting to incur costs) in all categories/stages. It is clear that those PIPs that will involve multiple stages, and include phase II and phase III trials, will be more expensive.

In relation to the number of clinical studies that are part of a PIP, there are also important differences in the number of sites and the locations of sites and associated wage differentials.

Figure 4 Distribution of PIPs by the number of clinical studies agreed upon



2.2.4.3 Number of paediatric subjects

The survey collected data on the number of paediatric trial subjects that were involved in phase II and phase III studies, recognising this can be an important cost driver. If a phase had not started, the number of paediatric trial subjects was reported as zero and if the phase was ongoing the number of paediatric trial subjects include the number of patients that had been involved up to that date. The data summary is presented in Table 4. We also note that in some instances, costs had already been accruing before paediatric trial subjects were enrolled. We understand this to be in relation to preparatory costs of screening as well as difficulties to recruit subjects. For example, the target age of paediatric subjects and the conditions for participation in paediatric trials play a role in recruitment and drive costs.

In our sample, on average, 66 [0-900] paediatric trial subjects participated in phase II clinical trials and, on average, 154 [0-2,000] paediatric trial subjects participated in phase III clinical trials. If the phase was completed, on average, 43 [1-154] paediatric trial subjects participated in phase II clinical trials and, on average, 292 [18-2,000] paediatric trial subjects participated in phase III clinical trials. Note that the median of paediatric trial subjects that participated in completed phases is similar to the median calculated for the overall sample. Moreover, it was found that the majority of paediatric trial subjects are located in the EU.

Table 4 Number of paediatric subjects involved in phase II and phase III clinical trials.

	Average	Median	Min	Max	Number of observations
Total number of paediatric trial subjects that participated in the phase II clinical trial(s)	66 (79% EU)	16	0	900	37
Total number of paediatric trial subjects that participated in the phase III clinical trial(s)	154 57% EU)	54	0	2,000	62
Total number of paediatric trial subjects that participated in the phase II clinical trial(s) - If phase is completed	43 (74% EU)	19	1	154	17
Total number of paediatric trial subjects that participated in the phase III clinical trial(s) - If phase is completed	292 (52% EU)	55	18	2,000	21

Table 5 presents a breakdown of the average estimated cost per subject. These calculations are based on values of individual PIPs and using data on both completed and incomplete R&D phases. This yields an average cost per subject of €377k and a median cost estimate of €77k for phase II; for phase III, we calculate an average cost of €244k and likewise a median cost estimate of €77k. The median estimates may be considered a more helpful indication of cost per subject[7]. We however recognise that the sample dataset underlying our cost estimate per subject for phase II and phase III trials involves large variations and thus significant uncertainties remain in these cost estimates.

Table 5 Estimated cost per subject, based on information on individual PIP and data on both completed and incomplete phases

	Average	Median	Minimum	Maximum	Number of observations
Phase II	€377k	€77k	€20k	€3.5m	27
Phase III	€244k	€77k	€1k	€4.0m	44

[7] The average cost estimates calculated using data on both completed and incomplete R&D phases are significantly higher than estimates that can be calculated using data on completed phases only: for phase II, the average number of subjects is 43, the average estimated cost of the trial is € 7.3m, and thus the average cost per subject is €170k. For phase III, the average number of subjects is 292, the average estimate cost of the trial is €15.7m and the average cost per subject is only €54k.

2.2.4.4 Duration of a PIP

The average planned duration of a PIP, from the date of initial application to the planned completion date, is 7 years [0-23] (calculation based on EMA data)[8] with a considerable variation between the expected duration of PIPs – as illustrated in Figure 5. It is also expected that the average duration of PIPs that are discontinued, based on the date of submission up to the point that they are discontinued, will be lower than 7 years.

Moreover, an analysis of the average duration of PIPs sorted by the initial submission year shows that the PIPs filed in the initial years of the Regulation, especially in 2008, had a lower than average expected duration (Table 6). It may well be that those PIPs were less burdensome (in cost and time) as many of these products had generated significant clinical data, and probably originate under Article 8. It should be noted that because only a relatively smaller number of PIPs were submitted in the first years following the enactment of the Paediatric Regulation, it is likely that the overall effect on estimated cost to industry is small.

The higher than average planned duration for PIPs submitted in the year 2010 is driven by a large number of PIPs in the therapeutic area Pneumology – Allergology. It is not known why the planned duration of this group of PIPs is significantly above average.

Figure 5 Distribution curve of the planned duration of PIPs, in years

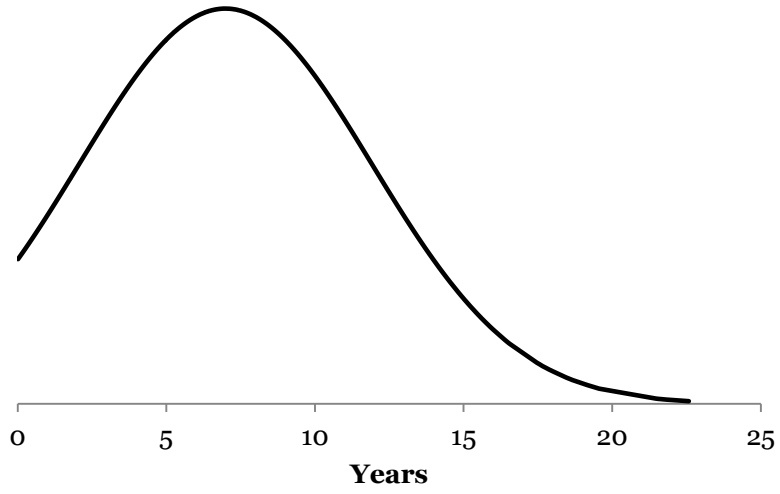


Table 6 Average planned duration of PIPs by submission year

Submission year	Average planned duration/ years
2007	5.2 (13)

[8] PIPs that had a planned completion date registered prior to the initial application date are excluded.

Submission year	Average planned duration/ years
2008	4.7 (24)
2009	6.4 (48)
2010	13.1 (125)
2011	6.7 (61)
2012	5.7 (87)
2013	6.0 (142)
2014	5.8 (145)
2015	5.6 (152)

Based on 797 PIPs, number of observations per year in parenthesis (source: EMA PIP database)

2.2.4.5 Therapeutic area

The cost of filing and executing a PIP is also related to the therapeutic area. For example, it will be more challenging to recruit clinical trial subjects for some indications in certain therapeutic areas than others, resulting in a notable difference in the average number of paediatric subjects involved in the trial. Table 7 presents a breakdown of the average cost incurred in different therapeutic areas, by R&D phase, calculated using data for completed phases only. The cost figures are merely indicative as it relies on a small number of observations and cost drivers other than the therapeutic area may be at play. However, it may well illustrate the degree of variation across a range of therapeutic areas. It shows, for example, that costs incurred in relation to Haematology-Hemostaseology are generally lower than the total average R&D costs. And, for example, costs related to infectious diseases are likewise below average R&D costs estimates but not the costs related to the development of a paediatric formulation, which are estimated to be higher than average.

Table 7 Average estimated cost incurred by therapeutic areas and R&D phase, in millions of euro (based on data for completed phases only)

	In-vitro studies and animal studies	Development of a paediatric formulation	Phase II paediatric clinical trials	Phase III paediatric clinical trials
Cardiovascular diseases		€ 1.2 [€0.3-€2.0]		
Infectious	€ 0.5 [€0.1-€1.2]	€ 3.2 [€0.6-€6.7]	€ 1.9 [€1.0-€3.7]	€ 12.5 [€3.0-€22.0]

	In-vitro studies and animal studies	Development of a paediatric formulation	Phase II paediatric clinical trials	Phase III paediatric clinical trials
diseases				
Endocrinology, -gynaecology-fertility-metabolism	€ 0.7 [€0.1-€1.6]	€ 0.6 [€0.5-€0.8]	€ 0.9 [€0.4-€1.7]	€ 5.7 [€1.0-€15.7]
Neurology	€ 2.5 [€1.7-€3.3]			
Oncology	€ 0.5 [€0.3-€1.0]			
Haematology-Hemostaseology	€ 0.1 [€0.0-€0.1]	€ 1.4 [€0.3-€3.0]	€ 2.5 [€0.3-€5.2]	€ 8.7 [€1.8-€15.4]
Overall average costs	**€ 0.8**	**€ 1.6**	**€ 7.3**	**€ 15.7**

Average estimated costs incurred by therapeutic areas are based on a minimum of two data points per PIP category

Figure 6 Average cost incurred in relation to in-vitro studies and animal studies, by therapeutic area

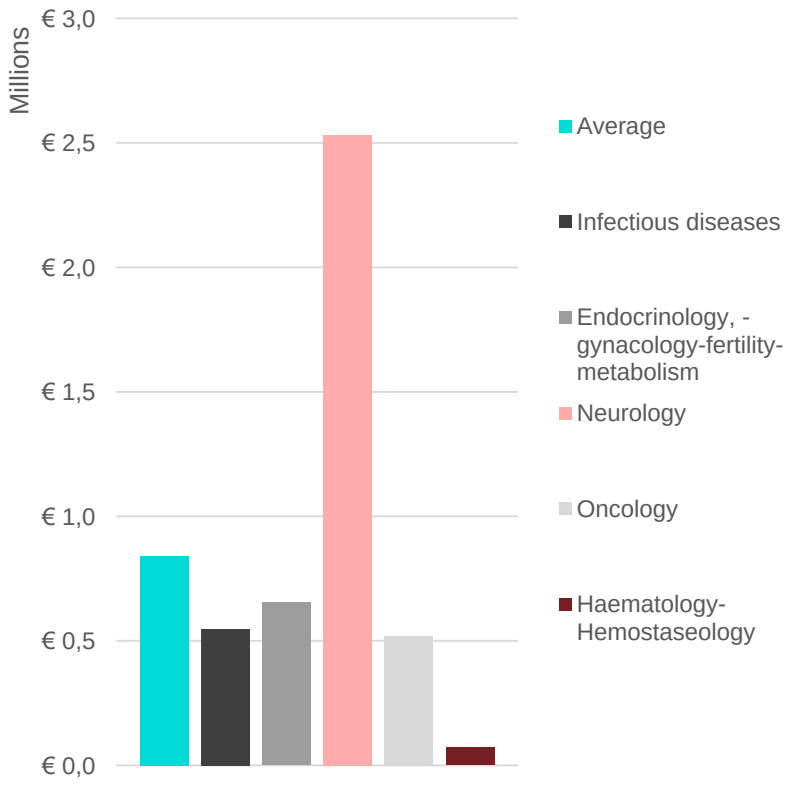


Figure 7 Average cost incurred in relation to the development of a paediatric formulation, by therapeutic area

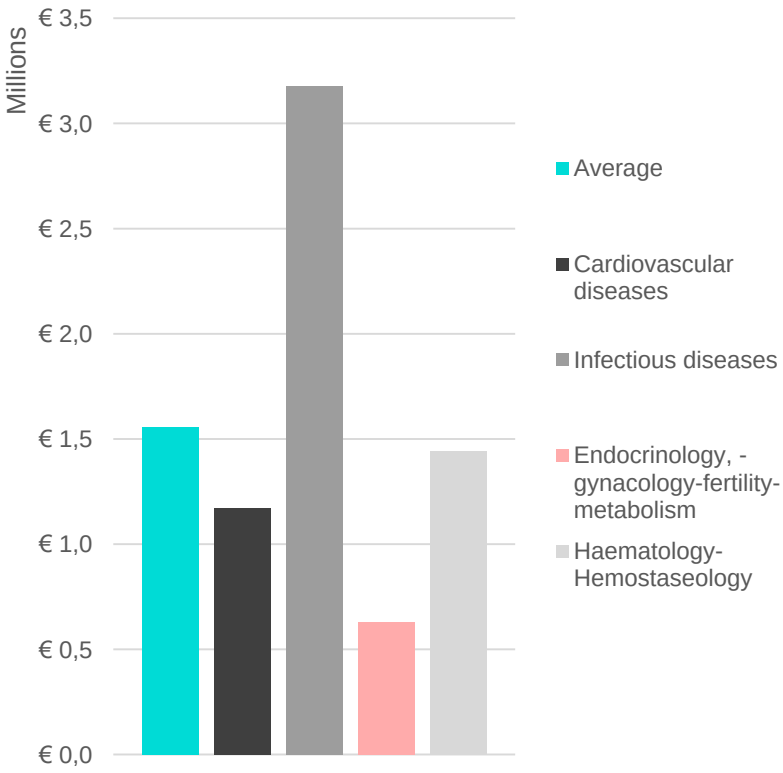


Figure 8 Average cost incurred in relation to phase II paediatric clinical trials, by therapeutic area

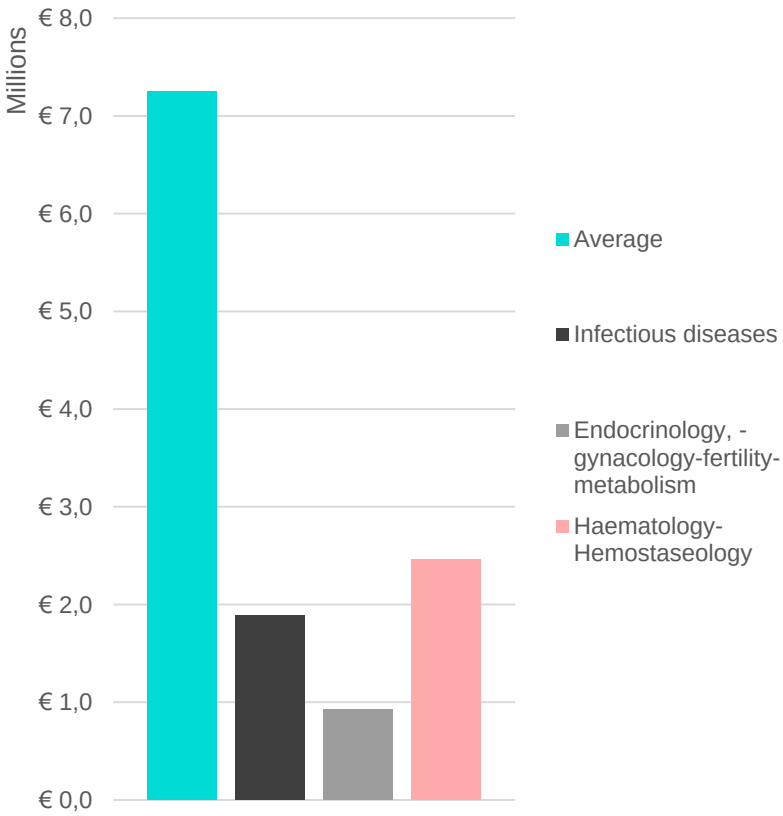
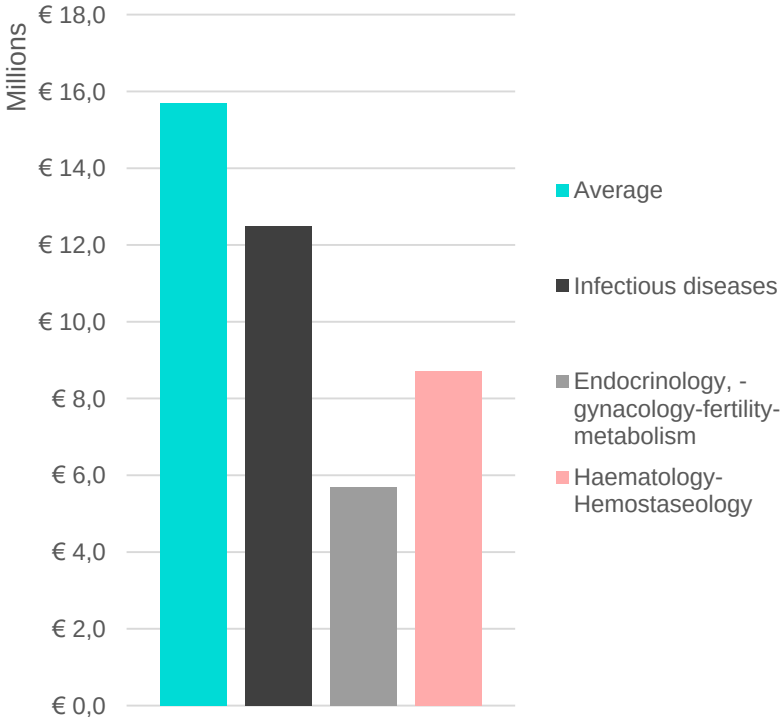


Figure 9 Average cost incurred in relation to phase III paediatric clinical trials



2.2.4.6 Collaboration with networks

Based on the survey results, 18% of PIPs involved a collaboration with a research network. This included informal networks and consultations with paediatricians and formal networks such as the European Paediatric Formulation Initiative (EUPFI), the Task-force in Europe for Drug Development for the Young (TEDDY), the Medicines for Children Research Network (MCRN), and the Innovative Therapies for Children with Cancer (ITCC). In some cases, there may have been a monetary benefit from engaging in research collaborations. It is likely that collaborations with academic partners not only help to drive more effective paediatric research but also test drugs within the paediatric population at a lower cost.

2.3 Comparison of costs under the US legislation

The US has a different approach than that of the European Union to engaging with the pharmaceutical industry. The US recognised the need for a paediatric exclusivity provision in the FDA Modernization Act in 1997. Later, the Pharmaceuticals for Children Act (BPCA, 2002) and Pediatric Research Equity Act (PREA, 2003) came to represent a two-tier system and the major cornerstones of the paediatric medicine development in the US. The FDA Safety and Innovation Act (FDASIA) made BPCA and PREA permanent in 2012. While PREA authorises the FDA to require paediatric assessments (triggered by a new drug application, or new indication, active ingredient, dosage form, etc and hence mandatory), BPCA provides a financial incentive to companies to voluntarily conduct paediatric studies under a paediatric Written Request (WR), often initiated by the sponsor. The WR considers public health benefits, availability of other medicinal products for the same indication, as well as the actual feasibility of the study design. Note that the initial Pediatric Study Plan (iPSP) is only required in PREA after the completion of adult Phase II trials. In addition, FDASIA also introduced the (transferable) Priority Review Voucher Program for rare paediatric disease indications. The US Government Accountability Office (GAO) published a report in March 2016 and concluded that since innovative medicinal product development typically takes 10 years before regulatory submission can take place, it may be too early to see the results of its effectiveness.[9]

There are two prominent studies published in the US that calculate the costs of paediatric clinical trials for the pharmaceutical industry (Li et al. 2007[10]; Baker-Smith et al. 2008[11]).

Li et al. (2007) selected one drug from each of the following therapeutic areas: cancer, central nervous system, cardiovascular system, psychiatry, endocrinology, gastro-intestinal system, infectious diseases and an 'other' category (based on EMA therapeutic area classifications). The costs for paediatric clinical trials were estimated separately for each drug. This estimation was based on detailed information regarding the clinical trials in the final study reports which were submitted to the FDA, and included investigative site costs, contract research organization costs, pharmaceutical company costs, and core laboratory costs in

[9] GAO-16-319. United States Government Accountability Office: Report to Congressional Committees. RARE DISEASES: Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program. March 2016

[10] Li, J.S. et al., 2007. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. *JAMA*, 297(5), pp.480–488. Available at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.297.5.480.

[11] Baker-Smith, C.M. et al., 2008. The economic returns of pediatric clinical trials of antihypertensive drugs. American Heart Journal, 156(4), pp.682–688.

relation to adult/mixed trials. The clinical trials for which costs were assessed included 13 to 1,088 patients, took 6 to 64 months and were conducted on 1 to 118 sites, most of them in the US. Additional details of the trials considered in the estimations included the pre-study preparation and recruitment, data processing, analysis, reporting and drug distribution as well as initiation visits, monitoring, management and close-out of sites. The cost estimation of these factors was based on three separate global cost and procedure benchmarking databases and an internal pricing tool of a laboratory service for those clinical studies that needed core laboratory services. Li et al. provided a 'low' and a 'high' estimate, with the authors stating that, according to their experience, the high estimate is more likely to be accurate in the context of paediatric clinical trials. Note that this approach differs from the approach taken in the current study where product-specific incurred costs were estimated by the sponsors of the trials.

Li et al. concluded that the costs for pharmacokinetic studies range between $655,139 to $7.1m (median $894,941) and between $655,829 to $21m (median $2.3m), respectively, and the costs for an efficacy study range between $1.8m to $12.9m (median $6.5m) – see also Table 8 for adjusted cost estimates. This resulted in a range of costs for a WR between $5.1m and $43.8m (median $12.3m), which included 1 to 8 clinical trials per request. After adjusting for macro-economic changes[12] this amounts to a cost per WR between €5.6m and €47.9m (median €13.5m). Based on the data presented in the study of Li et al., we calculate that the median cost per enrolled subject is €42.7k, which is lower than the median costs presented in this study in relation to phase II and phase III R&D trials, which is € 77k.

Some of the authors of the first study conducted a second analysis, focussing on nine drugs for the *same* indication, hypertension (cardiovascular diseases), in order to achieve a general estimate of paediatric trial costs for drugs with this clinical indication (Baker-Smith et al. 2008[13]). From 1997 to 2004, the FDA received final study reports for 12 antihypertensive drugs, and the authors included in their sample all of those drugs which had a completed final study report (24 in total) and were comparable in their clinical trial design, being all orally administered. 75% of the studies were conducted in children, the remaining 25%, which are bioequivalence/bioavailability studies, were conducted in adults. The authors estimated the costs and cash-outflows with the same method as in their first study, providing low and high estimates for each clinical trial. As in the previous study, the costs included investigative site costs, contract research organization costs, pharmaceutical company costs, and core laboratory costs. Not included were the costs of formulation changes, marketing costs and distribution costs. The clinical trials for this sample of drugs included 16 to 441 patients over 6 to 50 months and were conducted on 1 to 78 mostly US sites.

Estimated adjusted-costs per WR for these nine range from €4.2m to €15.5m (median €6.6m), which includes the cost of bioequivalence/bioavailability studies. 41% to 73% of costs of clinical trials were related to coordination (linked that the cost incurred by a coordinating centre), including the cost of site management and project management.

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[12] Costs adjusted for inflation capture the increase in inflation (21.4%) between 2005 (costs reported in the study are adjusted to 2005 US dollars) and 2015. We use http://www.usinflationcalculator.com/. Cost are converted from US dollar costs to Euros (exchange rate for 2015 - 0.9009). We have used https://www.oanda.com/currency/average

[13] Baker-Smith, C.M. et al., 2008. The economic returns of pediatric clinical trials of antihypertensive drugs. American Heart Journal, 156(4), pp.682–688.

As presented in Table 8, the adjusted-median cost for efficacy and safety clinical trials, similar to phase II trials, is lower for the study of Bakker-Smith et al (€4.7m) which looks at hypertension than the adjusted-median costs presented in Li et al. (€7.1m), which covers a range of drugs. Both figures are higher than the estimated median costs for phase II R&D trials that is presented in this study (€1.7m). Median costs for efficacy and safety clinical trials and pharmacokinetic studies per subject (see Table 8) are roughly less than half of the median cost estimates presented in this study in relation to phase II and phase III trials (€77k).

Table 8 Overview of estimated costs for 'Written Requests'

		Median and range Li et al. et al. 2007	**Median and range Baker-Smith et al. 2008**
Cost per written request	**Efficacy and safety clinical trials (phase II)**	€ 7.1m [€0m - €14.1m]	€4.7m [€2.3m - €14.1m]
	Pharmacokinetic studies	€1.0m [€0.7m - €7.8m] (single-dose) €2.5m [€0.7m - €23.0m] (multi-dose)	€0.9m [€0.6m - €2.0m]
Cost per subject	**Efficacy and safety clinical trials (phase II)**	-	€35k [€21k- €56k]
	Pharmacokinetic studies	-	€32k [€15k - €52k]

We recalculate the financial cost data per trial from our sample dataset and present the results along with the study of Li et al. We aggregate the cost elements of phase II, phase III and other R&D costs to reflect the overall R&D cost related to paediatric drug development and adjust this cost estimate for inflation and exchange rates. We thus compare this average cost estimate with the average cost estimate of presented earlier in the current study. Figure 10 presents an overview of the adjusted cost data of Li et al[14] in various therapeutic areas. Whilst the average costs presented in the current study are intended to reflect average cost to industry, it should be noted that the data from Li et al. is not intended to be representative of the industry. The adjusted average cost estimate based on the data of Li et al. amounts to €21m, higher than our €18m cost estimate for phase II, phase III and 'other' R&D costs. We likewise note the high variation in costs related to paediatric investigation for different drugs: ranging from €6m to €48m. However, when the US and EU cost estimates are compared *per study*, the variations become less pronounced (Figure 11). The average cost of a paediatric

[14] Costs are adjusted for inflation to capture the increase in inflation (24.27%) between 2005 (trial costs were estimated in 2015 US dollars) and 2015. We use http://www.usinflationcalculator.com/. Cost are converted from US dollar costs to Euros (exchange rate for 2015 - 0.9009). We have used https://www.oanda.com/currency/average. Figure 10 presents cost by therapeutic area. Data on indication from Li et al. is used to categorise the cost estimates using the therapeutic area categorisation used by EMA.

study according to Li et al is €7m, with individual therapeutic areas ranging from €3m to €11m, while the calculated cost per study is €6m in the current study.

Figure 10 Estimated costs of paediatric investigations (related to the development of a drug), based on Li et al. (2007)

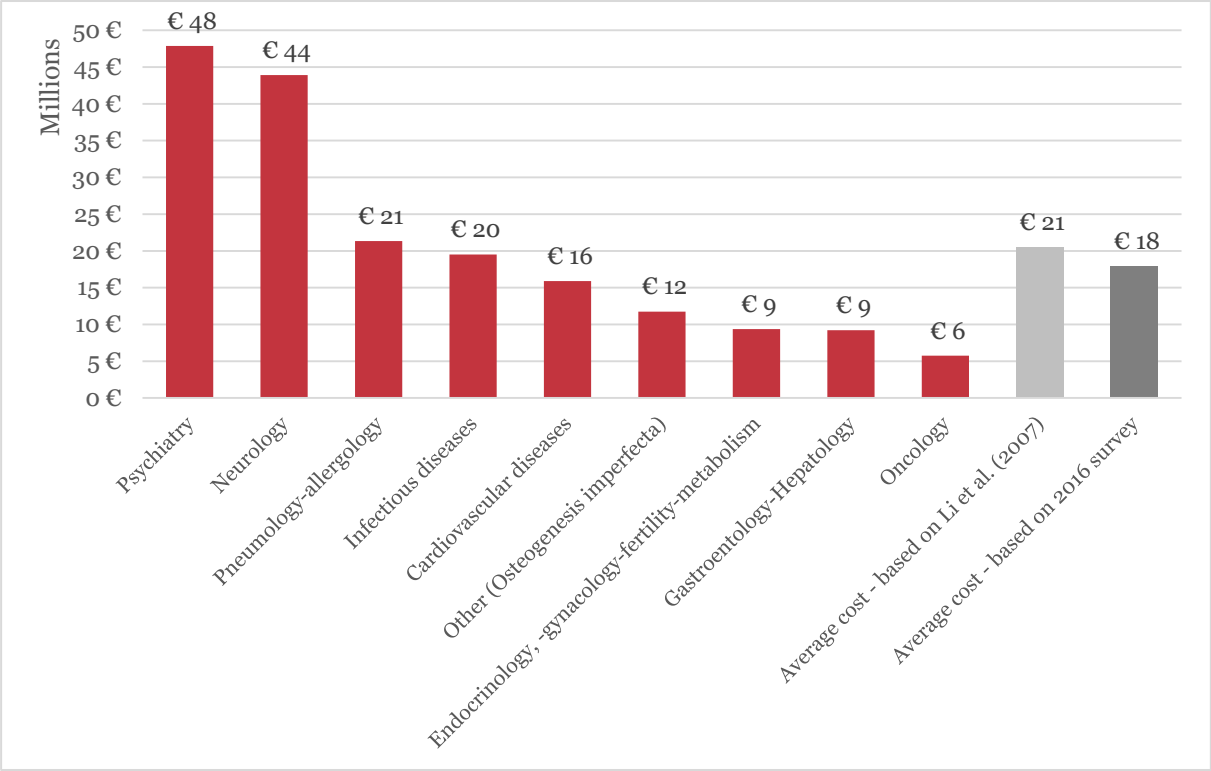
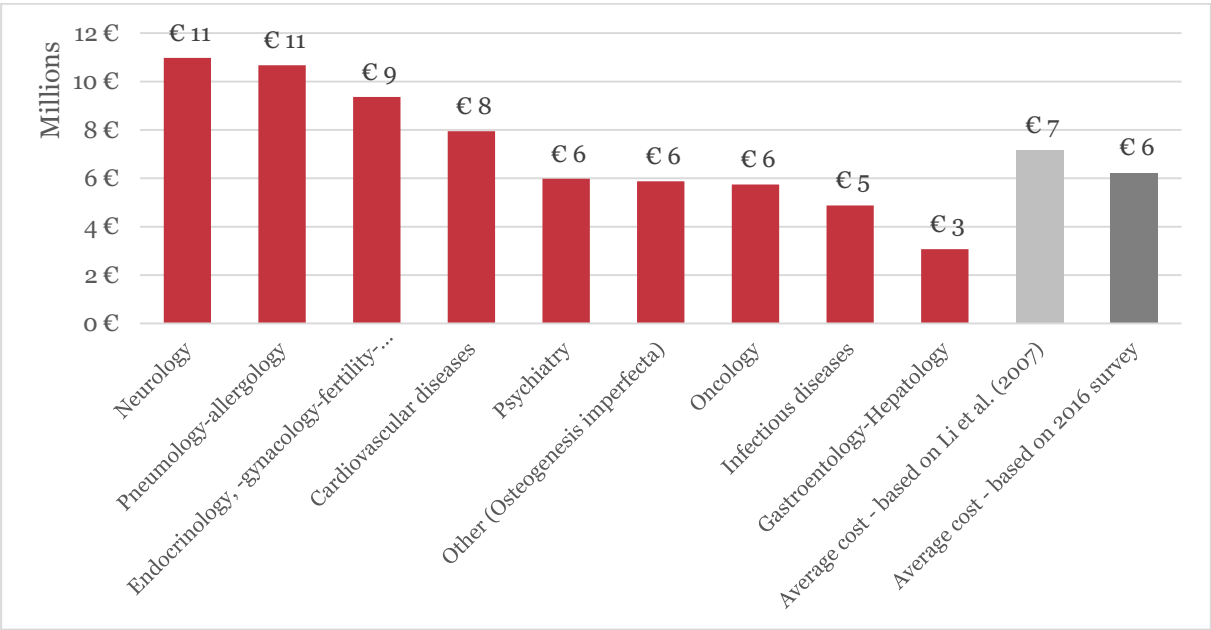


Figure 11 Estimated costs of a paediatric study, based on Li et al. (2007)



2.3.1 Harmonisation of submissions to EMA with submissions to the FDA

In 2007, EMA and FDA established the Paediatric Cluster to discuss (through monthly teleconference) product-specific paediatric development issues under a confidentiality agreement (now also joined by Japan, Canada and Australia). The objective of these exchanges is to enhance the science of paediatric trials (discussions on end points, safety and feasibility issues) and to avoid exposing children to unnecessary trials. Since 2007, the FDA and EMA have exchanged information on a total of 413 products and held 132 discussions on general topics.[15] A Common Commentary has been developed as a tool to inform paediatric trial sponsors about non-binding discussions at the Paediatric Cluster of products that have been submitted to both FDA and EMA.

Our survey to industry also asked if the data from a PIP was also used to apply to the FDA. A breakdown of the results is presented in Figure 12. Data from 54% PIPs were suggested to be (partially) used to apply to the FDA and/or discussions with the FDA were in progress. This includes submissions as part of PREA and data included in waiver applications. Only a small proportion (3%) of these PIPs were discontinued, possibly after submission to the FDA.

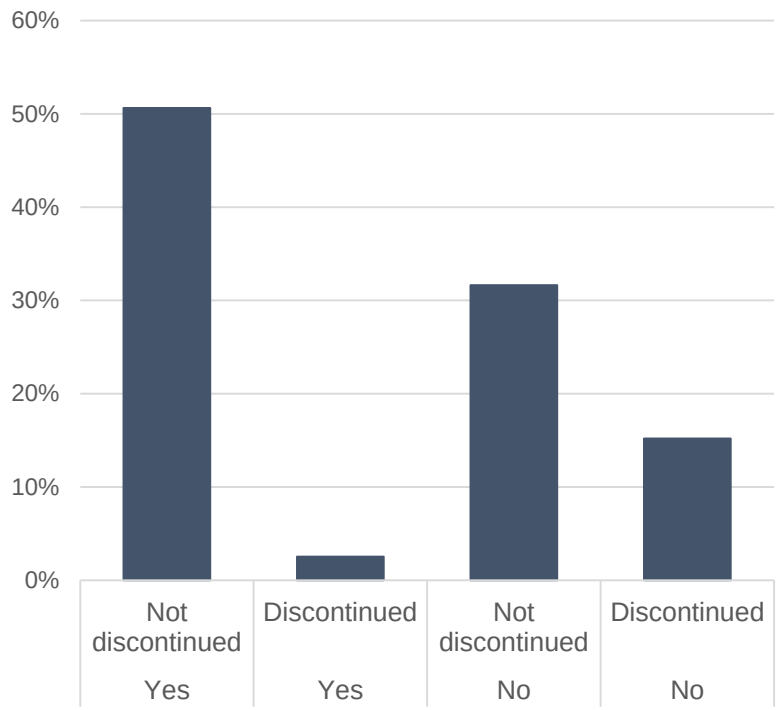
Data for the remaining PIPs was reported to not be used for applying to the FDA – a larger proportion of these PIPs (15%) were discontinued. Reasons for not using the PIP data as part of a submission to the FDA include the following:

- PIP was discontinued before application was filed with the FDA
- PIP applicant received a waiver for orphan drugs
- PIP was initiated post-US approval
- FDA and EMA did not agree on a harmonised plan – different study design requested

Despite some of the difficulties in harmonising the submissions to EMA with those to the FDA, there are substantial opportunities for data sharing. This joint approach has the potential to contribute to lower regulatory costs to companies overall and thus enhanced efficiency.

[15] http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm

Figure 12 Distribution of PIPs that use or plan to use data generated for submission to the FDA (yes) versus those that do not use data for submission to the FDA (no)



2.4 Comparison of R&D costs of paediatric trials with adult population trials

Two studies specified particularities of paediatric clinical trials, which are likely to lead to higher costs for these trials compared to the ones with adult patients (Mathis & Rodriguez 2009[16]; Upadhyaya et al. 2009[17]). These included the limited number of patients available for trials, since the physiological changes in children require conducting separate studies for different age groups and to assess the patients' unique growth and development regularly during clinical trials. One industry survey respondent remarked that "the many scientific, ethical and practical complexities involved have traditionally made paediatric studies more challenging, costly and time-intensive than those conducted in adults".

This suggests that *cost per trial subject* is likely to be higher for paediatric studies. In this section we compare the average cost estimates presented in this study with that available in the literature looking at the cost involved in adult/mixed trials.

DiMasi et al. (2016)[18] provide estimates for industry 'out-of-pocket' clinical period costs for investigational compounds. Table 9 presents a breakdown comparing the paediatric cost

[16] Mathis, L. & Rodriguez, W., 2009. Drug therapy in pediatrics: A developing field. *Dermatologic Therapy*, 22(3), pp.257–261.

[17] Upadhyaya, H.P., Gault, L. & Allen, A.J., 2009. Challenges and Opportunities in Bringing New Medications to Market for Pediatric Patients. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(11), pp.1056–1059.

[18] DiMasi, J., Grabowski, H., and Hansen, R. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics, 47.

estimates with the data of DiMasi et al, for phase II and phase III. Cost estimates of DiMasi et al. are adjusted for inflation and exchange rate differences[19].

The result shows that the average cost of paediatric phase II and phase III clinical trials are only a small fraction (14% for phase II and 7% for phase III) of the cost estimates published by DiMasi et al. It is possible that part of the €14.4m allocated to 'other R&D costs' element in the data survey of the current study (Table 3) may be linked to phase II or phase III clinical trials. However, even with full attribution of these costs to either clinical trial phases, the average cost of a paediatric trial would remain significantly lower than the average cost estimate of adult/mixed clinical trial in the work of DiMasi et al.(2016). It should also be noted that the standard deviations presented by DiMasi et al. are comparatively high suggesting a relatively larger variation in the underlying data.

One possible explanation for the cost differential is that adult clinical trials may involve a relatively larger number of trial subjects. Also, clinical trials for adult population is more likely to involve double blind placebo controlled confirmatory studies, which, depending on the therapeutic area, may differ in size and scope. Additional analysis of available evidence is needed to compare the costs per subject of paediatric trials with those of adult population trials.

Table 9 Comparison of estimated cost of a paediatric clinical trial compared with average-out-of-pocket clinical period costs, in millions of euros

	Phase II paediatric clinical trial cost	**Phase II clinical trial cost (based on DiMasi et al)**	**Phase II paediatric clinical trial cost as a percentage of phase II clinical trial cost**	**Phase III paediatric clinical trial cost**	**Phase III clinical trial cost (based on DiMasi et al)**	**Phase III paediatric clinical trial cost as a percentage of phase III clinical trial cost**
Average	€ 7.3	€ 53.7	14%	€ 15.7	€ 234.0	7%
Median	€ 1.7	€ 41.0	4%	€ 1.5	€ 183.2	1%
Standard deviation	14.3	50.8		22.4	153.3	

Source: average-out-of-pocket clinical period costs are based on Di Masi et al. (2016)

[19] Costs adjusted for inflation capture the increase in inflation (1.7%) between 2013 (trial costs were estimated in 2015 US dollars) and 2015. We use http://www.usinflationcalculator.com/. Cost are converted from US dollar costs to Euros (exchange rate for 2015 - 0.9009). We have used https://www.oanda.com/currency/average

3 The value and the costs of the rewards and incentives

This chapter presents the results of the analysis of the economic value of the rewards and incentives provided under the Paediatric Regulation in relation to the six-month SPC prolongation (article 36), the 'orphan' reward (article 37) and the PUMA reward (article 38). First presented is the methodological framework, which was developed to assess the overall value and costs of the rewards provided by the Regulation, followed by the results of the analysis for each of the three rewards.

3.1 Methodological framework

In this section, we first present and discuss the main principles underlying the methodological framework that we developed for analysing the value and costs of the rewards. Thereafter, we present the methodological framework, as well as the data and approach used in the analysis.

3.1.1 The main principles underlying the methodological framework

The focus of the analysis is on the value and costs of the three main rewards to industry provided by the Regulation. The concept of value and costs covers three main elements:

1. The Regulation aims to stimulate investments and research with regard to the development of medicines for children. In accordance with recital 2 and recital 6 of the Regulation (EC) no 1901/2006 "many of the medicinal products currently used to treat the paediatric population have not been studied or authorized for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population. (…) The establishment of a system of both obligations and rewards and incentives has proved necessary to achieve these objectives."
2. The Regulation rewards pharmaceutical companies via a (temporary) protection against the regular forces of competition in the pharmaceutical market. This protection is arranged via the creation or extension of temporary exclusivity rights. Under the Regulation these rights are data exclusivity, market exclusivity and market protection.
3. As a result of the temporary exclusivity rights, the pharmaceutical companies could profit from a longer period of protection. In practice this means that the market entry of new (generic) competition is delayed and that originator companies can charge 'monopoly prices' for a longer period.

3.1.1.1 Addressing market failures[20]

The main driver for the introduction of the Regulation was the absence of sufficient numbers of suitable and authorised medicinal products for the paediatric population. The reason for the lack of paediatric medicines is related to the existence of market failures that have inhibited medicinal product development. Medicine for children can be regarded, to some extent, as a public good that contributes to the health and wellbeing of current and future end

[20] Based on: Ecorys, 'Competitiveness of the EU Market and Industry for Pharmaceuticals - Volume I: Welfare Implications of Regulation', December 2009, Chapter 3 and 4; and Ecorys 'How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies', November 2015.

users. The willingness for originator companies to invest in R&D in relation to new medicine is reduced because competitors will be able to trace the product components at the time the product is launched, hence eroding potential profits the originator can accrue. The so-called free-riders forgo the large R&D investment made by the originator in relation to product development. In the case of paediatric medicines, the attractiveness to invest is often reduced further when the target group of patients is small in size and heterogeneous.

According to economic theory these market failures can be partially resolved by the introduction of temporary market exclusivity rights (e.g. patent protection), which allow the originator to accrue monopoly level profits from the product developed for a longer period of time. The additional profits are a reward for the (risky) R&D investments made in relation to product development.

3.1.1.2 The creation or extension of temporary exclusivity rights[21]

In the European Union, the development of new medicinal products can be protected by a patent that is filed at the national patent office of individual Member States or via a single patent application at the European Patent Office (EPO). In the latter case, which is used by the majority of pharmaceutical companies, a national validation of the 'European patent' is still necessary. The European patent is granted by the EPO for each Member State where the patent owner wishes the patent to exist and to be enforceable.[22] In Europe (and the US), patent protection may be obtained for up to 20 years,[23] starting from the moment the patent application is filed at the patent office of the territory concerned.[24] Note that to compensate the R&D investment made in relation to a new chemical entity (NCE), the patent can be extended by a maximum of 5 years (i.e. 25 years of patent protection in total). However, patent protection does not guarantee that the 'product information' (which is also valuable to the society as a whole) cannot be used during the period of patent protection. Within the limitations of the patent right, the information is available in the public domain and can be used by others for further R&D.

For medicinal products the specific market protection consists of (i) an eight year period of 'data exclusivity'[25] and (ii) a two year period of 'market protection'[26]. This means that a

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[21] Based on: Ecorys, 'Competitiveness of the EU Market and Industry for Pharmaceuticals - Volume I: Welfare Implications of Regulation', December 2009, Chapter 3 and 4; and Ecorys 'How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies', November 2015.

[22] European Commission, DG Competition, 2009, Pharmaceutical Sector Inquiry, final report. The criteria EPO uses for granting a patent are based on the European Patent Convention (EPC) of 1973 and later amendments to the EPC.

[23] These 20 years is based on WTO-agreements. The 'Agreement on Trade Related Aspects of Intellectual Property Rights' (TRIPS) determines that patent protection must be available for inventions for at least 20 years. See also: https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm.

[24] The Sector Inquiry states that this period of 20 years reflects the assessment by the legislator that the end of this period is the point in time where the cost to society of continued patent protection (lack of competition, prices above the marginal costs, extra profits to the patent holder), starts exceeding the benefits (research, investments, etc.). See: European Commission, DG Competition, 2009, Pharmaceutical Sector Inquiry, final report.

[25] Data exclusivity: period of time during which a company cannot cross-refer to the data in support of another marketing authorisation; See: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf.

[26] Market protection: period of time during which a generic, hybrid or biosimilar cannot be placed on the market, even if the medicinal product has already received a marketing authorisation. In case of a 'new indication', the period of market protection will be extended to three years. Available via: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf.

generic application can be submitted to the EMA eight years after the patent is filed and a generic product can be launched after ten years. Another type of protection exists for medicines with an orphan designation which have received a marketing authorisation. For these medicines, no other application for a marketing authorisation for a similar product in the same therapeutic indication will be considered by the competent authority for a period of ten years.[27] The period of market exclusivity granted under the orphan reward (article 37, see also section 3.3) is extended by two years if the application for a marketing authorisation includes the results of all studies conducted in compliance with an agreed Paediatric Investigation Plan (PIP). The PUMA reward (article 38, see section 3.4) gives the manufacturer an 8-year period of data exclusivity. After these 8 years, there is an additional period of two years of market protection.

In the 1990s, a supplementary protection certificate (SPC) was created for medicinal products.[28] The main reason for this was to provide the originator companies an extension of the protection granted by the primary patent, due to the usual delay between the filing of a patent application and the authorisation for market launch, which substantially reduced the period in which a patent owner can commercially exploit the patent for a medicinal product. Not all patents are eligible for an SPC. The SPC has a variable duration (from zero to a maximum of five years), and as a result the holder of both a patent and a SPC should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorisation to be placed on the market in the European Union.[29]

Following article 36 it is possible to reward the holder of a patent or SPC with a six-month extension of the duration of the SPC (see also section 3.2). This reward can be granted if an application for marketing authorisation includes the study results as agreed in the PIP. Please note that the extension period of six months was not undisputed at the time of drafting and adopting the Paediatric Regulation. While the proposal of the Commission for the Regulation contained the six-month period, some Member States suggested shortening the six-month SPC prolongation (e.g. to three months) because the measure would delay the entry of generic medicines too much. Others suggested determining variable extension periods which should depend on the financial returns. Finally, the six-month SPC prolongation was retained, in combination with the obligation to conduct an assessment of the economic impact, provided enough information is available.[30]

3.1.1.3 Economic value of the rewards

Under the Paediatric Regulation pharmaceutical companies may benefit from eg a prolongation of the SPC, granting the companies market exclusivity for a longer period of time. The resulting higher profits, ie the economic value of the rewards, for these pharmaceutical originator companies also results in higher costs for healthcare. The impact on the pharmaceutical companies and healthcare system is described in the following sections.

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[27] EMA, see slide 18: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf.

[28] Council Regulation No 1768/92 concerning the creation of a supplementary protection certificate for medicinal products.

[29] European Commission, DG Competition, 2009, Pharmaceutical Sector Inquiry, final report, p. 111-113.

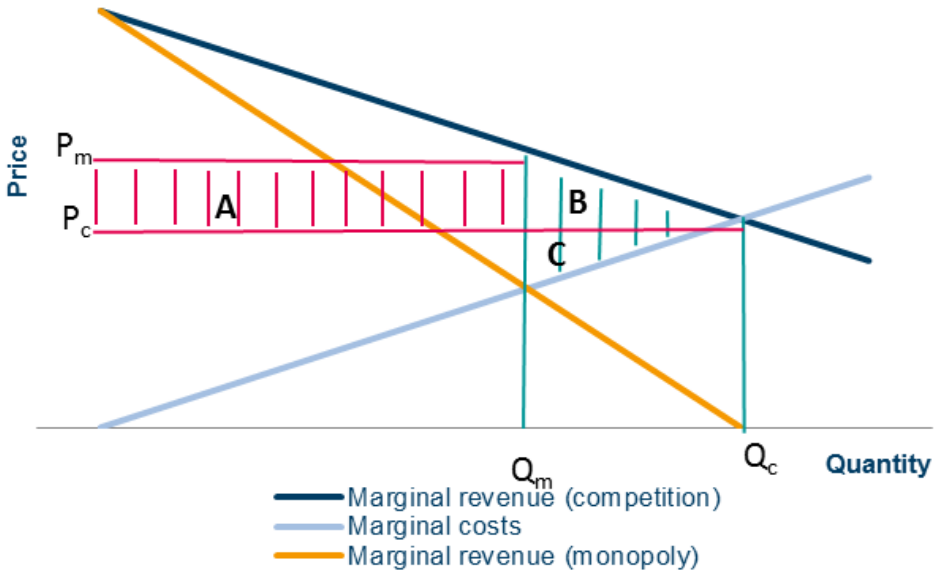
[30] Dunne, 'Regulation on medicines for paediatric use' in: Paediatric respiratory reviews (2007) 8, 177–183.

3.1.2 *Methodological framework for estimating the economic value of exclusive rights*[31]

The assessment of the economic value of the reward is based on the following key assumption. As a result of the market exclusivity extension, there is a delay in the shift from the (higher) monopoly prices to the (lower) competitive market prices. This delay in the change of price is calculated to represent the economic value of the rewards.

The standard economic theory states that in a competitive market situation, the price of a product equals the marginal costs of that product. The main explanation for this equilibrium is that, due to the price pressure from other competitors, it is not possible for a company to charge a relatively higher price without losing market share. In a situation of market exclusivity competitive market pressure is absent (or very small) and the monopolist is able to charge above the marginal cost price. This higher price corresponds, in comparison with the competitive market situation, with a lower quantity of product sales. This model is presented in the figure below.

Figure 13 Monopoly vs competitive situation



Note in a competitive situation, the price (Pc) equals the marginal costs and results in a certain quantity of sold products (Qc). In a monopolistic situation, the monopolist can charge a higher price (Pm) which leads to a lower quantity sold (Qm). The underlying assumption is here that a company, who wants to maximize the profit, should set the output (quantity) on the level that the marginal revenues equal the marginal costs.

A monopolist benefits from a higher price but, because prices are relatively higher, forgoes some opportunity to sell. The 'surplus' is represented by rectangle A (profit for the company) and triangle C (loss for the company) in the figure above. As a result of the monopoly price and quantity, consumers lose a 'surplus' of rectangle A and triangle B in the figure.

[31] Based on: Pindyck, R.S. and Rubinfield, D.L., 'Microeconomics', 5th edition, 2001, chapter 10.

- Rectangle A represents the profit accrued by the monopolist and the loss for the (potential) consumer.
- Triangle B and C represent the deadweight loss from monopoly power and loss to society: even if the monopoly profits are regulated to zero, the surplus for the society as a whole is lower than in a competitive situation. [32]

The standard economic theory as described above is used to capture the impact from the Paediatric Regulation on pharmaceutical companies and on the healthcare system. In this case, the market is first represented by a monopolist that has exclusivity rights and then shifts towards a competitive market situation as a result of generic entry. In the situation of the Paediatric Regulation, the granted exclusivity rights prolong the monopolistic market situation.[33]

3.1.3 Estimating the economic value of exclusivity rights

The methodological framework which is used in this study is a combination of the economic principle of the 'deadweight loss from monopoly power', the applied research of Nelson (2012) and the approach presented by DG COMP (2009), see Appendix C. In order to assess the 'economic value' of the rewards, two dimensions need to be taken into account.

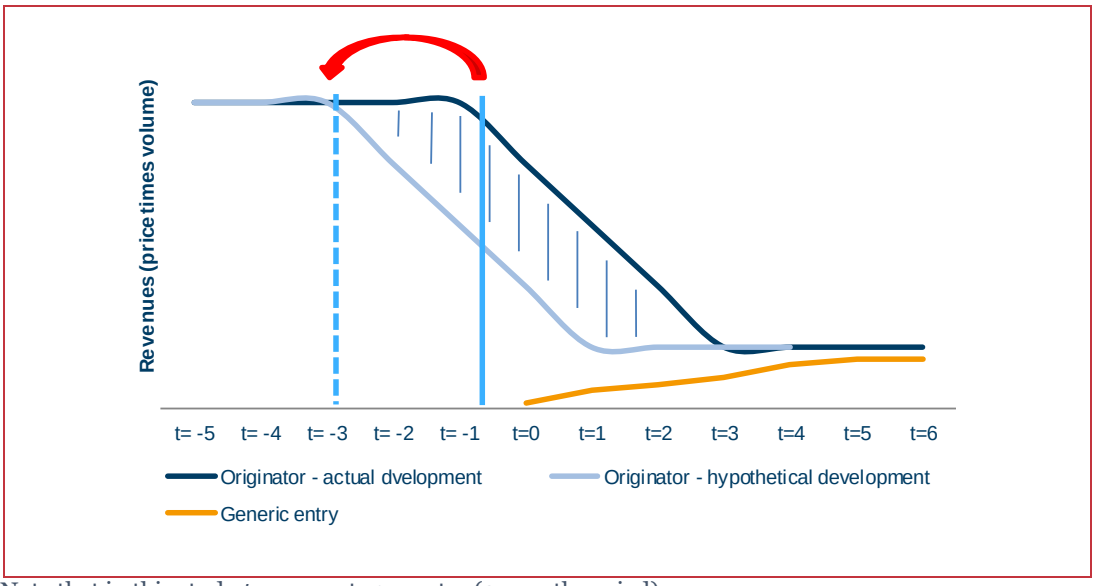
- The rewards compensate the originator companies with a longer period of protection from the introduction of competing generic medicines and policies which favour the prescription of generic medicines
- Because the introduction of generic medicines is delayed, society does not benefit from increased competition and lower prices for the duration of the exclusivity extension

This is illustrated in the figure below.

[32] Pindyck, R.S. and Rubinfield, D.L., 'Microeconomics', 5th edition, 2001, section 10.4.

[33] In case of the PUMA reward the monopolistic market situation is not prolonged, but created: it did not exist before the granting of the PUMA reward.

Figure 14 Calculation of the economic value (hypothetical situation)



Note that in this study *t* represents 1 quarter (3-month period)

The figure above shows the actual revenue development of an originator product with a reward.[34] The revenue starts to drop at the moment the exclusivity right ends (vertical line at *t*=0) and a generic producer enters the market. At a certain moment (*t*=5) the market reaches a new equilibrium. Without the additional reward the generic producer can enter the market earlier and the revenue drop of the originator will start (six month) earlier. In combination with the actual revenue development of the originator company, the shaded area represents the 'economic value'. This is a temporary 'benefit' for the originator company and a temporary 'loss' for the society. In line with the approach of DG COMP (2009), we shift the actual curve ("*Originator – actual development*") six month to the left ("*Originator – hypothetical development*") and estimate the difference between the two curves.[35]

Note that this is a simplified model for illustration purposes. In reality, there are several other factors which influence the economic value of the reward which may affect the revenue/price drop curves across EU Member States.

- When interpreting national sales data from comparative perspective, it is important to account for the proportion of patients on treatment and the manufacturer price. The originator company may follow a different **pricing strategy** by anticipating the moment the exclusivity right expires and lower the price gradually or keep the price stable for a longer period if there is still no generic product.
- The economic value of the reward can also be influenced by the availability of competing (generic) products which function as an alternative or **substitute**. If there is no generic

[34] This examples refers to (i) a SPC extension, or (ii) an orphan reward. In case of the PUMA-reward, there is a reversed dynamic (the start instead of the end of an exclusive right). See also section 3.5.

[35] Note that there is another approach to calculate the economic value. In this approach one calculates, for the two quarters before the SPC-expiry, the difference between (i) the actual revenue of the originator (dark blue line) and (ii) the revenues of the originator in the new equilibrium (dotted red line). The area of this rectangle represents the 'economic value'. The result of this second approach is equal to the primary approach, the project team tested this for a few products.

medicine available, the revenues of the originator product may remain stable after the expiration of the exclusivity right. This factor also relates to the existence of clinical guidelines and the **willingness of patients to switch** between different brands of medicines. A recommendation on using a particular drug is very likely to have a positive effect on the sales of the drug. The results from the interviews conducted in this study confirm that in some Member States patients want to continue using the (branded) medicines they are familiar with, despite a substantial price difference. If this is the case, the pressure on the originator company to lower the price is limited.

- Finally, **national (reimbursement) policies and regulation** are important factors that influence prices. European countries use different approaches regarding the pricing of generics. Some countries (e.g. France) use prescriptive pricing (regulated prices), other countries (e.g. Sweden, Netherlands) apply free pricing[36]. Different approaches to the pricing of generics among European countries can lead to substantial variation between originator and generic prices[37]. Also, countries may emphasise the prescription of generic products through national policies (e.g. Sweden[38]). Beside that there exist incentives to keep the originator price high in certain countries, due to the fact that other countries use those prices as a reference price in determining the reimbursement price they pay.

In sections 3.2-3.4 we present the results of estimating the economic value per type of reward. In addition to calculating the economic value a number of other relevant elements were determined. These elements are in line with the analysis of DG COMP as described in Appendix C:

- Generic entry and time to entry - The actual level of generic entrants after the loss of exclusivity (probability of generic entry and number of generic entrants) as well as the time it requires a generic producer to enter the market with a generic product after the loss of exclusivity;
- Price change - The change in (branded) prices due to generic entry. The estimations are based on the price level prior and after the loss of exclusivity. The price change is calculated for the long-run and for specific periods (if possible: 1-4 years after the loss of exclusivity);
- Generic penetration - The shares of generic producers (in terms of volume[39]) in the period after the loss of exclusivity and in comparison to the shares of the originators;
- Substitution effects - Where relevant we will also pay attention to substitution effects, which implies that within the same therapeutic class, volume is shifting from one product (INN) to another.

See Appendix C for more details on the approach taken to determine these effects.

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[36] Simoens, S., 2012, *A review of generic medicine pricing in Europe*, GaBI Journal, 1(1), p. 8-12.

[37] McKee, M., Stuckler, D. and Martin-Moreno, J.M., 2010, *Protecting health in hard times*, BMJ, 341:c5308.

[38] Hassali, M. et al., 2014, *The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use*. Saudi Medical Journal. 22:491-503.

[39] In this specific case we choose volume (number of sold single units) over revenues, due to the fact that the price differences between branded and generic products disturb the overall picture. The volume data is more accurate in terms of the relative share of generic and branded products after the loss of exclusivity.

3.2 The six-month SPC prolongation (article 36)

Under article 36 of the Regulation it is possible to reward the holder of a patent or SPC with a six-month extension of the duration of the SPC (see also section 3.1). This reward can be granted if an application for marketing authorisation includes the study results as agreed in the PIP.[40]

The section below provides a brief description of the actual use of the reward in practice. The section thereafter presents the results of the analysis, which covers the generic entry, the envisaged price changes, the level of generic penetration, substitution effects and finally the economic value.

The analysis for this section is based on IMS Health data provided by the European Commission for period between 2008-2014 (the last available data point is the 3rd quarter of 2014). The scope and limitations of the dataset are described in Appendix C. The analysis in this report covers products which (i) received a SPC extension in the period between 2007-2012 and (ii) lost their exclusivity before the third quarter of 2014. This choice for this period is related to the need to have enough observations in the data after the loss of the exclusivity. The data available for the study covered 14 products which received the SPC extension in this period (see also Table 10). However, five products received the reward but were still under protection in the third quarter of 2014. For one product, available data did not allow to make a distinction between protected and non-protected products with an SPC extension. See Appendix C for a detailed description. The remaining eight products are used in the analysis. The analysis also builds on interviews with pharmaceutical industry.

3.2.1 Actual use of the six-month SPC prolongation

Over the period 2007-2015 the SCP reward was granted to 32 different medicinal products. In total there were 311 extensions, as not all medicinal products received the six-month extension in each Member State.[41] For *Losartan* for example the producer received the SPC-reward in eleven countries, while for *Caspofungin* this concerned 19 countries. An overview is presented in Table 10 below.[42] The data available for the study included 14 products but for the analysis only used eight products were included. Products are excluded from the data analysis due to patent expiry after 2015 and in one case (Drug D) a product was excluded from the data analysis due to differentiation issues; the SPC product could not be isolated from the non-SPC products.

[40] Regulation (EC) No 1901/2006 on medicinal products for paediatric use, in combination with the Council Regulation No 1768/92 concerning the creation of a supplementary protection certificate for medicinal products.

[41] European Medicines Agency; the annual publications by the Paediatric Committee (PDCO) and the 5-year Report to the European Commission (2012 on the experience acquired as a result of the application of the Paediatric Regulation (EMA/428172/2012). The EMA indicated that these annual (survey) reports are not complete: it is estimated they have a coverage of approximately 80% of the actual number of granted SPCs.

[42] Note that from the total number of paediatric drugs, we excluded (i) duplicates, (ii) applications with pending status. Drugs with associated names were merged.

Table 10 Number of SPCs per medicine per year in the EU-28: 2007-2012 and 2007-2015

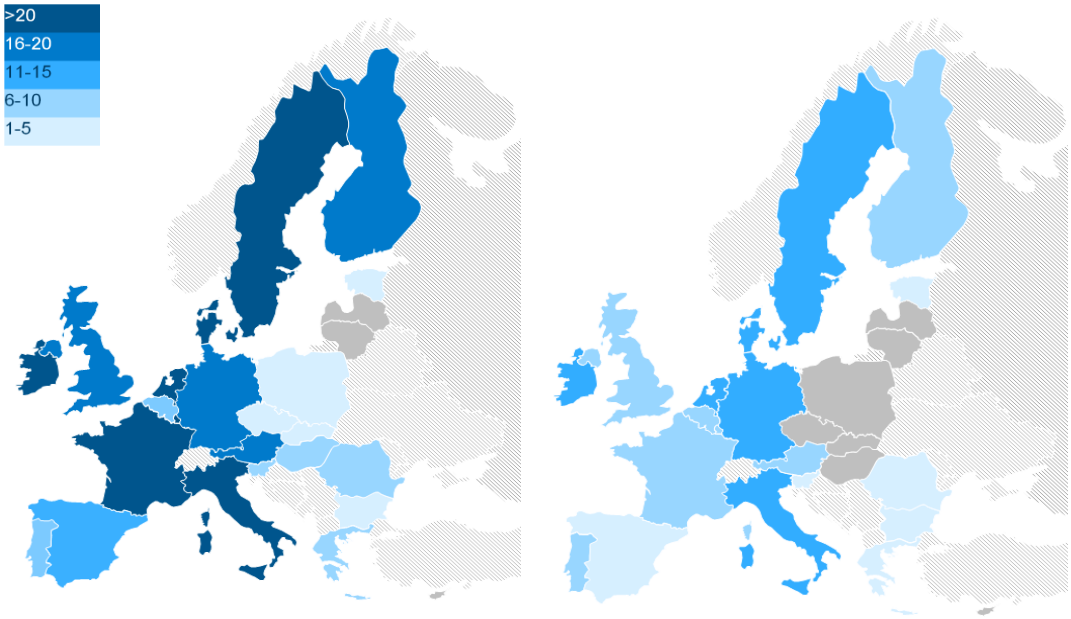
No	Marketing authorisation holder	Brand name	INN	2007-09	2010	2011	2012	Total 07-12	2013	2014	2015	Total 07-15
1	Bristol-Myers Squibb Pharma EEIG	Orencia	Abatecept		7	6	3	16			1	17
2	AbbVie Ltd	Humira	Adalimumab								13	13
3	AstraZeneca AB	Arimidex a.a.n.	Anastrazole	2	10			12				12
4	Otsuka Pharmaceutical Europe Ltd	Abilify	Aripiprazole							1		1
5	Actelion Registration Ltd	Tracleer	Bosentan								11	11
6	Merck Sharp & Dohme	Cancidas	Caspofungin	7	6	1	1	15	3		1	19
7	Sanofi BMS	Plavix a.a.n.	Clopidogrel			4	5	9				9
8	Janssen-Cilag International NV	Prezista	Darunavir								9	9
9	Bristol-Myers Squibb Pharma EEIG	Baraclude	Entecavir							4	7	11
10	Pfizer Limited	Enbrel	Etanercept				5	5	4	1	1	11
11	Merck Sharp & Dohme	Ezetrol a.a.n.	Ezetimibe								4	4
12	Novartis Europharm Limited	Glivec	Imatinib						1	7	5	13
13	Janssen Biologics B.V.	Remicade	Infliximab				6	6	1	1		8
14	Novo Nordisk A	Levemir	Insulin detemir								3	3
15	Sanofi-Aventis Deutschland GmbH	Lantus Optisulin	Insulin-glargine				4	4	5	1		10
16	Les Laboratoires Servier	Corlentor/Procoralan	Ivabradine								5	5
17	Pfizer	Xalatan a.a.n.	Latanoprost			11		11				11
18	Merck Sharp & Dohme Inc.	Cozaar a.a.n.	Losartan	10	1			11				11

No	Marketing authorisation holder	Brand name	INN	2007-09	2010	2011	2012	Total 07-12	2013	2014	2015	Total 07-15
19	Merck Sharp & Dohme	Singulair	Montelukast			4	5	9				9
20	Boehringer	Viramune	Nevirapine			2	8	10				10
21	Merck Sharp & Dohme (Europe) Inc.	Maxalt	Rizatriptan				11	11	1		1	13
22	AstraZeneca AB	Crestor a.a.n.	Rosuvastatin								7	7
23	J. Uriach y Compañía, S.A.	Rupafin	Rupatadine							2	2	4
24	Pfizer Limited	Tygacil	Tigecycline								9	9
25	Boehringer	Spiriva	Tiotropium bromide						13	1		14
26	Otsuka Pharmaceutical Europe Ltd	Samsca	Tolvaptan						8			8
27	Alcon Laboratories (UK) Ltd	Travatan	Travoprost								3	3
28	Sanofi Pasteur MSD	Gardasil	Vacc. papillomavirus							3	7	10
29	Roche Registration Limited	Valcyte	Valganciclovir							2	3	5
30	Novartis Pharma AG	Diovan a.a.n.	Valsartan		10	2		12				12
31	Pfizer Limited	Vfend	Voriconazole							6	10	16
32	Novartis	Zometa a.a.n.	Zoledronic acid		11	2	1	14				14
Total				19	45	32	49	145	36	29	102	31

Based on the Annual Reports to the European Commission (prepared by the Section Paediatric Medicines of EMA). Notes: (i) the numbers represent the decisions to grant a SPC-extension; the actual period to use the reward may be years later; (ii) the granted SPCs for atorvastatin, colesevelam, paclitaxel albumine and sitagliptin were not reported in the Annual Reports. The list including these four products was published after conducting the analysis.

In terms of the geographical spread of the SPC extensions, there is a clear distinction between the Member States who joined the EU after 2003 (EU-13) and the other Member States (EU-15). The countries with the highest number of SPCs are located in West and North Europe (EU-15). According to interviewees, this relates to original design of the patents in the EU-15 Member States: SPC extensions fit better with the patents granted in these Member States.

Figure 15 Geographical spread of granted SPCs in the EU in 2007-2015 (left) and 2007-2012 (right)



Based on the annual reports to the European Commission, prepared by the Paediatric Medicines Office of EMA

3.2.2 Generic entry and time to enter

We assessed the actual level of generic entrants after the loss of exclusivity, as well as the time it requires a generic producer to enter the market. The analysis covers the level of generic entry per country and per product. The results of the analysis are presented in the Table below. Based on the data analysis of the eight selected products two main observations can be made:

Generic entry - the analysis shows that for all eight products there exists generic entry. The number of entrants[43] varies between products and countries. The largest numbers of entrants can be found in countries such as France, Germany, and Italy. In these countries, the number of entrants is substantial for certain products - Drug A, Drug E, Drug F, Drug H and (in some cases more than 20 companies enter the market). However, other countries, like The Netherlands, Ireland, and especially Sweden, also show a substantial number of generic entrants, although their number varies across the different drugs.

[43] These are individual companies. The data is cleaned for duplications.

Time to enter –the data shows that the average time it takes a generic producer to enter the market with a generic product (after the loss of exclusivity) is relatively short. Again, there exist substantial differences between countries and products. For all products there is generic entry in the first quarter in at least five countries. In Germany, Italy, Ireland, the Netherlands, Sweden and the UK market entry is visible for nearly all products[44] (with a very few exceptions) in the first quarter after the loss of exclusivity.

Table 11 Level of generic entrants after the loss of exclusivity

International Non-proprietary Name	Drug E	Drug H	Drug F	Drug A	Drug C	Drug B	Drug G	Drug I
Austria								
First entry (quarter)	Q1	Q1	Q1				Q1	Q1
No. of entries in 1st quarter	8	2	12				2	4
No. of entries in 2nd quarter	4	7	12				11	6
Max. no. of generic entries until Q3/14	16	16	20				14	11
Belgium								
First entry (quarter)	Q1		Q1		Q1			
No. of entries in 1st quarter	3		7		1			
No. of entries in 2nd quarter	5		7		1			
Max. no. of generic entries until Q3/14	9		10		2			
Finland								
First entry (quarter)	Q1	Q1	Q1				Q1	
No. of entries in 1st quarter	8	5	11				6	
No. of entries in 2nd quarter	13	6	16				7	
Max. no. of generic entries until Q3/14	19	9	16				9	
France								
First entry (quarter)	Q1		Q1			Q1	Q1	Q1
No. of entries in 1st quarter	18		13			4	14	3
No. of entries in 2nd quarter	20		18			4	15	4
Max. no. of generic entries until Q3/14	26		28			5	26	10
Germany								
First entry (quarter)	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1

[44] With a few exceptions: Ireland (Drug C, Drug B), the Netherlands (Drug I), UK (Drug A).

International Non-proprietary Name	Drug E	Drug H	Drug F	Drug A	Drug C	Drug B	Drug G	Drug I
No. of entries in 1st quarter	26	17	26	22	4	11	21	14
No. of entries in 2nd quarter	35	21	33	27	6	15	26	20
Max. no. of generic entries until Q3/14	47	34	47	29	6	18	32	31
Ireland								
First entry (quarter)	Q1	Q1	Q1	Q1			Q1	Q1
No. of entries in 1st quarter	8	6	9	10			11	8
No. of entries in 2nd quarter	11	7	10	12			12	9
Max. no. of generic entries until Q3/14	16	16	14	17			16	9
Italy								
First entry (quarter)	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1
No. of entries in 1st quarter	11	21	12	13	0	7	13	5
No. of entries in 2nd quarter	13	22	15	18	1	7	17	9
Max. no. of generic entries until Q3/14	31	30	27	36	2	10	32	12
Netherlands								
First entry (quarter)	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q2
No. of entries in 1st quarter	9	8	9	2	3	6	6	0
No. of entries in 2nd quarter	9	7	11	8	3	7	7	2
Max. no. of generic entries until Q3/14	10	9	13	9	4	7	9	4
Portugal								
First entry (quarter)					Q1		Q1	Q1
No. of entries in 1st quarter					3		1	1
No. of entries in 2nd quarter					3		1	5
Max. no. of generic entries until Q3/14					4		22	11
Romania								
First entry (quarter)								Q1
No. of entries in 1st quarter								2
No. of entries in 2nd quarter								13
Max. no. of generic entries until Q3/14								17
Spain								
First entry (quarter)				Q1	Q1	Q1		

International Non-proprietary Name	Drug E	Drug H	Drug F	Drug A	Drug C	Drug B	Drug G	Drug I
No. of entries in 1st quarter				24	5	9		
No. of entries in 2nd quarter				25	6	10		
Max. no. of generic entries until Q3/14				32	7	14		
Sweden								
First entry (quarter)	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1
No. of entries in 1st quarter	8	9	12	8	0	7	7	2
No. of entries in 2nd quarter	18	8	18	14	0	7	9	4
Max. no. of generic entries until Q3/14	23	15	23	17	0	11	15	11
UK								
First entry (quarter)	Q1	Q1	Q1		Q1	Q1	Q1	Q1
No. of entries in 1st quarter	9	5	6		5	3	7	6
No. of entries in 2nd quarter	9	5	11		5	2	7	6
Max. no. of generic entries until Q3/14	12	12	12		6	5	11	10

Based on IMS Health data. Note that Q3/2014 is the end of the sample data. Drug D was eliminated from the analysis.

3.2.3 The envisaged price changes (branded and generic products)

In a competitive market, the pressure of generic entry is expected to lower the prices of branded products after the loss of exclusivity. The change in price level prior and after the loss of exclusivity was assessed[45] (if possible: 1-4 years after the loss of exclusivity). Please note that again there exist significant differences between countries and products.

The data analysis shows that the price drop of branded products often starts in the first quarter after the loss of exclusivity. However, this price drop is often relatively limited (up to 10-20%). During the first and second year (after the loss of exclusivity) the branded prices decrease further, but with larger differences between products and countries. For example, in the Netherlands the price drop after two years varies from 42-60%, while in Germany this varies between 4 and 24%. When the branded prices are weighted for the sold volumes, the price drops in the end are often substantial (in some cases up to > 95%). The underlying data shows that branded products often keep a higher price than the generic competitor but that the sold volumes of branded products are very low.

For most of the selected products, the starting price of the generic entrant after the loss of exclusivity is significantly lower than the price of the branded products. Italy is an example of a rather aggressive generic pricing strategy: in the first quarter after the loss of exclusivity the generic prices are 30-40% of the original branded price (relative price reduction of 60-70%).

[45] The price change is calculated for the long-run and for specific periods (if possible: 1-4 years after the loss of exclusivity).

At the end of the data period (Q3/2014), a lot of generic prices are 10-30% of the original branded price.

3.2.4 The level of generic penetration

The loss of the exclusivity results in the entry of relatively cheap generic products and (often) in a substantial drop in the prices of branded products. As can be expected, the generic entry will also have an influence on the market share of the originator product. In the data analysis, we assessed the level of generic penetration: the relative share of generic products in the total volume (branded and generic products) in the period after the loss of exclusivity.

The findings show that the level of market penetration of generic products differs per country and per product. In some cases, the share of generic products in the total volume is above 70-90% (e.g. Sweden and the Netherlands), while in other cases the level of generic penetration is much lower (e.g. Belgium and Italy). There seem to be two main explanations for these differences. First, the national policies in relation to the prescription and reimbursement of generic products differ. In the interviews conducted it was confirmed that, especially in Sweden and the Netherlands, the use of generic products is lobbied for after the loss of exclusivity. For Italy, several interviewees indicated that the 'push' towards generic drugs is much softer and that patients often have a preference for the branded product they are familiar with. Second, the generic penetration seems to be related to the price strategy of both the generic and the originator product. In the UK for example, the price for generic products for Drug B is only 5% below the originator price (which also shows a relatively small price drop of 5-12% after the loss of exclusivity).

3.2.5 Substitution effects

The sales of a medicinal product are influenced by the presence or absence of other products with the same active substance or which are in the same therapeutic class (Anatomical Therapeutic Chemical (ATC)). E.g. a new product can reduce the volume of a product which is already on the market. These effects are called substitution effects. We distinguish two types of substitution effects: within the same active substance or with other active substances.

If present, the substitution effect can be derived from a decrease in volume. The variation (in index numbers) of the volume data per product is presented in Table 12. The reference volume is the volume of the 1st quarter of 2008. Variation of the volume is expected in a dynamic market. Normally, the volume will increase as time passes, because of market penetration. When the volume substantially decreases, it may be due to substitution effect. When a volume decreases with more than 20% (<80% in Table 12), desk research was conducted to confirm or reject the presence of a substitution effect. The two products with a volume decrease of more than 20% are Drug A and Drug C.

Table 12 Substitution effects (based on volume)

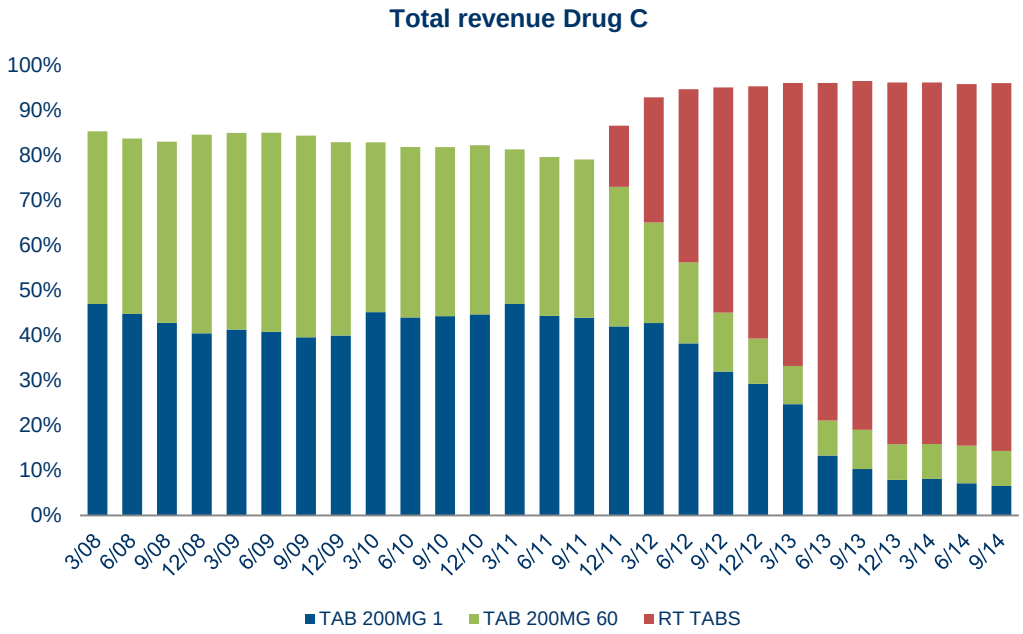
INN	Minimum	Maximum	Difference	Mean
Drug A	73.20%	133.40%	60.20%	109.10%

INN	Minimum	Maximum	Difference	Mean
Drug B	100.00%	168.10%	68.10%	140.20%
Drug C	31.90%	125.70%	93.80%	88.10%
Drug D	91.50%	114.80%	23.30%	103.40%
Drug E	80.40%	113.50%	33.00%	99.40%
Drug F	99.00%	165.30%	66.30%	131.90%
Drug G	97.60%	153.10%	55.50%	124.10%
Drug H	100.00%	113.20%	13.20%	107.10%
Drug I	86.00%	135.50%	49.50%	108.50%

Based on IMS Health data. Note: the volumes include both adult and paediatric usage.

In case of Drug A, the decrease of the volume was not constant. The volume recovered within a couple of quarters. However, the volume decrease of Drug C was substantial. In case of Drug C, a substitution is taking place from the moment a new tablet with the same active substance enters the market (see Figure 16 below). Drug C is an anti-HIV drug with a six-month paediatric extension until July 2013. After patent expiry, lower revenues of Drug C due to generic entry is expected. However, from the last quarter of 2011, the revenues were already decreasing. This is caused by the entrance of extended-release tablets. The volume of these tablets was increasing to the detriment of the normal tablets (200-mg). These extended-release tablets were protected by a new patent. Therefore, the potential market for the generic companies was reduced, because the patients were switching to another agent. This can be considered as a substitution effect (with the same active substance).

Figure 16 Substitution effect of Drug C (illustrating the revenues over time)



Based on IMS Health data. Notes: (i) the normal tablets of 200-mg were sold per single unit (blue) through hospitals and sold per 60 units through retail (green); (ii) the red product refers to new extended-release (RT) tablets; (iii) the revenues are based on list prices, the actual prices may be different (iv) the revenues include both adult and paediatric usage.

3.2.6 Economic value

In section 3.1 we described the overall methodology to assess the 'economic value' of the rewards. In the situation of the SPC-extension, the granted reward implies that the loss of the exclusivity is six months later than the situation without reward. Based on the available data we estimated per product and per country the economic value which the SPC extension represents. The methodology how this was calculated is described in Appendix C. The results of the data analysis are shown in the tables below. Please note that the time the market needed to reach a new equilibrium differs per country and per product and that in some cases there is no new equilibrium yet.

Table 13 Estimation of the economic value of the SPC-extension (in thousands of euro), by member state

Country	6-month revenue	Revenue with SPC extension	Revenue without SPC extension	Economic value	Economic value as a % of 6-month revenue
Austria	18,388	56,971	47,420	9,551	51.9%
Belgium	6,190	18,388	16,274	2,114	34.2%
Finland	11,286	24,372	17,719	6,653	58.9%

France	158,533	390,639	307,833	82,806	52.2%
Germany	277,522	703,345	566,845	136,500	49.2%
Ireland	16,246	48,270	41,084	7,187	44.2%
Italy	138,990	314,522	232,905	81,616	58.7%
Luxembourg	1,511	4,132	3,524	607	40.2%
Netherlands	71,025	146,274	86,918	59,356	83.6%
Portugal	9,388	24,204	19,527	4,677	49.8%
Spain	56,411	117,504	94,949	22,556	40.0%
Sweden	28,669	54,571	30,167	24,404	85.1%
UK	118,070	304,956	226,100	78,857	66.8%

Based on IMS Health data. Notes:(i) the revenues are based on list prices, the actual prices may be different; (iii) revenues include both adult and paediatric usage. (Slovenia is excluded for reasons of confidentiality)

Table 14 Estimation of the economic value of the SPC-extension

	International on-proprietary Name	**Economic value as a % of 6-month revenue**	**Time to equilibrium**	**Equilibrium**
Austria	Drug E	49.5%	8 quarters	
	Drug H	57.2%	6 quarters	
	Drug F	39.9%	8 quarters	
	Drug G	56.6%	7 quarters	
Belgium	Drug E	68.1%	8 quarters	
	Drug F	27.7%	8 quarters	
	Drug C	46.5%	5 quarters	No
	Drug B	8.7%	5 quarters	No

	International on-proprietary Name	Economic value as a % of 6-month revenue	Time to equilibrium	Equilibrium
Finland	Drug E	59.5%	8 quarters	
	Drug H	63.2%	6 quarters	
	Drug F	61.5%	8 quarters	
	Drug G	53.5%	7 quarters	
France	Drug E	51.8%	8 quarters	
	Drug F	45.5%	8 quarters	
	Drug B	22.9%	5 quarters	No
	Drug G	65.2%	7 quarters	
	Drug I	7.2%	6 quarters	No
Germany	Drug E	71.2%	8 quarters	
	Drug H	10.9%	6 quarters	
	Drug F	26.5%	8 quarters	
	Drug A	43.9%	7 quarters	No
	Drug C	22.9%	5 quarters	No
	Drug B	46.0%	5 quarters	No
	Drug G	47.4%	7 quarters	
	Drug I	56.5%	6 quarters	No
Ireland	Drug E	36.2%	8 quarters	
	Drug H	43.6%	6 quarters	
	Drug F	41.2%	8 quarters	

	International on-proprietary Name	Economic value as a % of 6-month revenue	Time to equilibrium	Equilibrium
	Drug A	60.4%	7 quarters	No
	Drug G	29.7%	7 quarters	
Italy	Drug E	71.2%	8 quarters	
	Drug H	20.2%	6 quarters	
	Drug F	57.7%	8 quarters	
	Drug A	54.2%	7 quarters	No
	Drug C	50.6%	6 quarters	No
	Drug B	52.7%	5 quarters	No
Luxembourg	Drug E	62.1%	8 quarters	
	Drug H	60.1%	6 quarters	
	Drug A	36.4%	7 quarters	No
	Drug C	47.6%	5 quarters	No
	Drug B	0.0%	5 quarters	No
	Drug G	43.2%	7 quarters	
Netherlands	Drug E	93.6%	8 quarters	
	Drug H	78.7%	6 quarters	
	Drug F	91.9%	8 quarters	
	Drug A	75.4%	7 quarters	No
	Drug C	47.4%	5 quarters	No
	Drug B	55.2%	5 quarters	No

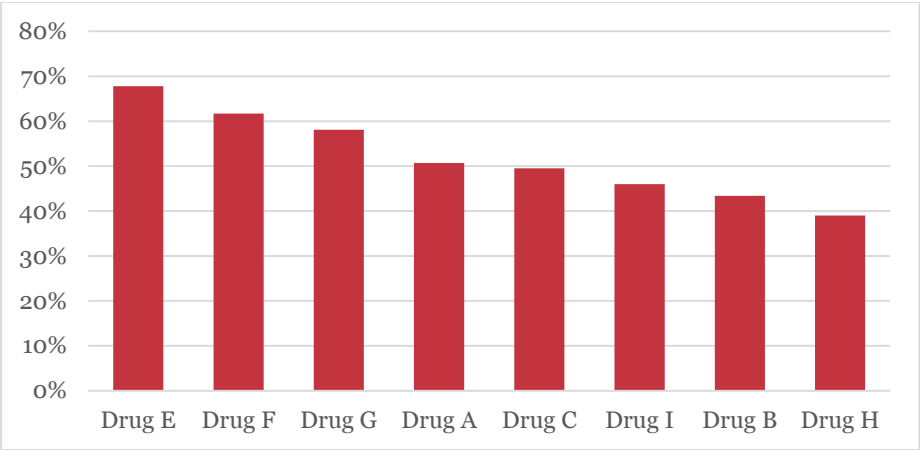
	International on-proprietary Name	Economic value as a % of 6-month revenue	Time to equilibrium	Equilibrium
	Drug G	86.1%	7 quarters	
Portugal	Drug C	438%	5 quarters	
	Drug G	50.3%	7 quarters	
Slovenia	Drug A	31.0%	7 quarters	No
Spain	Drug A	39.3%	7 quarters	No
	Drug C	52.4%	5 quarters	
	Drug B	23.7%	5 quarters	No
Sweden	Drug E	87.5%	8 quarters	
	Drug H	79.8%	6 quarters	
	Drug F	92.7%	8 quarters	
	Drug A	88.9%	7 quarters	No
	Drug B	68.3%	5 quarters	No
	Drug G	87.5%	7 quarters	
	Drug I	60.9%	6 quarters	No
UK	Drug E	79.2%	8 quarters	
	Drug H	47.9%	6 quarters	
	Drug F	88.8%	8 quarters	
	Drug I	37.1%	6 quarters	No

Based on IMS Health data. Notes:(i) the revenues are based on list prices, the actual prices may be different; (ii) revenues include both adult and paediatric usage; (iii) Drug D was eliminated from the analysis.

The table shows the estimated economic value in absolute terms and as percentage of the revenue in the half year (last two quarters) before the loss of exclusivity. The analysis shows that the economic value varies between products and countries. In stabilised market

situations, the economic value as a percentage of 6-month revenue vary between 10.9% (Germany – Drug H) and 93.6% (The Netherlands – Drug E). Figure 17 shows the variation in economic value, as a percentage of 6-month revenue per INN for the available countries.

Figure 17 Estimated economic value as a percentage of 6-month revenue, by INN



Based on IMS Health data. Notes: Revenues include both adult and paediatric usage.

Table 15 Economic value per product (column 2-5: x €1,000)

INN (# of included countries)	6-month revenue	Revenue with SPC ext.	Revenue without SPC	Economic value	Economic value as % of 6-month revenue
Drug A (8)	[redacted]	€ 270,309	€ 212,187	€ 58,122	50.7%
Drug B (8)	[redacted]	€ 65,646	€ 51,541	€ 14,105	43.4%
Drug C (7)	[redacted]	€ 26,271	€ 16,916	€ 9,355	49.5%
Drug E (11)	[redacted]	€ 540,988	€ 394,491	€ 146,497	67.8%
Drug F (10)	[redacted]	€ 458,454	€ 353,237	€ 105,217	61.7%
Drug G (9)	[redacted]	€ 451,678	€ 338,457	€ 113,221	58.1%
Drug H (9)	[redacted]	€ 208,701	€ 177,518	€ 31,183	39.0%
Drug I (4)	[redacted]	€ 189,866	€ 150,317	€ 39,548	46.0%
Total	**€ 913,432**	**€ 2,211,913**	**€ 1,694,664**	**€ 517,249**	**56.6%**

Based on IMS Health data. Notes: (i) between brackets is the number of countries covered in the analysis; (ii) revenues include both adult and paediatric usage; (iii) Drug D was eliminated from the analysis.

3.2.7 Extrapolation of the data

Due to limitations in the availability of data and in the data itself (see Appendix C), it was not possible to calculate for all countries and products the 'full' economic value of the reward.

We used the available data to make an extrapolation in order to assess the (magnitude of the) 'full' economic value of the reward. Please note that this extrapolation is based on

assumptions and that the actual economic value may differ from our estimations. The extrapolation is done in two steps.

- The first step is to estimate the economic value of the reward for the countries that are missing in the current set of eight products. Although in these countries an SPC-extension was granted, the dataset available for the study did not include data on these countries. Based on the 'revenue and economic value per capita'[46], the 6-month revenue and the economic value for the missing countries was estimated[47]. In the table below we show per INN the estimated economic value for the increased number of countries (the new number of countries is mentioned in the third column). The new estimated economic value, €628m, increased with 22% compared to the original estimated economic value of €517m.
- The second step in the extrapolation is to include the (four) products for which the period of exclusive rights, including the SPC-extension period, ended within the research period taken into account (December 2015), which is after the date of the dataset available for the study (third quarter 2014). We also included Drug D, for which the data did not allow to make a distinction between protected and non-protected products with an SPC extension. Based on the total population in the specific countries associated with the specific year in which the patent expires and 'revenue and economic value per capita' of the eight products in our dataset (see Table 16), we made an estimation of the 6-month revenue and the economic value of the SPC reward for the products. Based on this second step in the extrapolation, the adjusted economic value, €926m, increased with 79% in comparison to the original estimated economic value of €517m. Please note that the therapeutic areas of autoimmune diseases, diabetes mellitus and antipsychotics are not covered in the original set of eight products, which increases the uncertainty of the extrapolation.

Table 16 Extrapolated economic value per product for all countries (column 4 and 5: x €1,000)

INN	Therapeutic area	No. EU MS	6-month revenue (x 1,000 €)	Economic value	Economic value as % of 6-month revenue	Time to stabilization	Equil-ibrium?
Drug A	[redacted]	9	117,571	59,599	50.7%	7 quarters	Yes
Drug B	[redacted]	13	42,922	18,623	43.4%	5 quarters	Yes
Drug C	[redacted]	10	25,535	12,629	49.5%	5 quarters	Yes
Drug E	[redacted]	12	219,703	149,003	67.8%	8 quarters	No
Drug F	[redacted]	11	173,315	107,019	61.7%	8 quarters	No

[46] The economic value per capita is based on the calculated economic value per product and country, divided by the total population in the specific countries associated with the specific year in which the patent expires. The population is based on Eurostat-data.

[47] For the missing countries, the economic value is calculated by multiplying the average 'economic value per capita' with the population size.

INN	Therapeutic area	No. EU MS	6-month revenue (x 1,000 €)	Economic value	Economic value as % of 6-month revenue	Time to stabilization	Equil-ibrium?
Drug G	[redacted]	12	318,272	184,862	58.1%	7 quarters	No
Drug H	[redacted]	11	85,183	33,196	39.0%	6 quarters	No
Drug I	[redacted]	14	138,335	63,617	46.0%	6 quarters	Yes
Total			**1,120,836**	**628,548**	**56.1%**		
Average			**140,105**	**78,569**			

Based on IMS Health data. Note: revenues include both adult and paediatric usage.

Table 17 Extrapolated economic value per product, patent expiry before 31-12-2015 (column 4 and 5: x €1,000)

INN	Therapeutic area	No. of countries	6-month calculated revenue	Economic value SPC extension
	8 products (see table above)	N/A	1,120,836	628,548
Drug J	[redacted]	8	105,808	58,898
Drug K	[redacted]	10	143,744	80,015
Drug L	[redacted]	11	152,006	84,614
Drug M	[redacted]	1	27,232	15,159
Drug D	[redacted]	9	104,709	58,286
Total			**1,654,335**	**925,521**

Based on IMS Health data. Note: revenues include both adult and paediatric usage.

3.2.8 Limitations

With regard to estimating the economic value, a number of specific considerations need to be made.

- It is important to emphasise that the analysis is to some extent determined (and limited to) by the type and quality of the data that is available. As the steps for the extrapolation of the data show, the dataset available for the study is not including data on all products and /or countries which - in an ideal situation - would have been part of our dataset. The need to use assumptions results in uncertainty about the estimations. This margin of error in (especially) the extrapolation is strengthened by the fact that individual medicines often differ significantly in terms of strategic (pricing) behaviour of the originator and generic company and underlying market dynamics.
- Further, it is uncertain to what extent the available data is reflecting a fully realistic situation. The list prices for example (as used in the IMS Health database), are hardly used in practice. In some countries additional margins are added on top of the list prices for service providers, such as for example pharmacists. At the same time, pharmaceutical companies may negotiate reimbursement prices with national health authorities and

health insurances, which may result in a discount on the prices of the medicines. Despite these opposite price dynamics, we expect that the list price as presented in the IMS Health database is an underestimation of the 'real' price which at the end is paid by the health care payer. This would imply that also the calculated economic value of the SPC reward is an underestimation of the actual economic value. Uncertainty also exists in relation to the reported volumes in the IMS Health dataset. For some products and/or countries the dataset (only) contained hospital or retail data. This implies that in reality the volumes (and also the revenues) are higher than the reported values in the dataset and that the calculated economic value of the SPC-reward is an underestimation of the actual economic value. Within the scope of this study (and the available dataset), it was not possible to assess the magnitude of these (presumed) underestimations.

- A third consideration is that a substantial share of the economic value of the SPC-reward lies in the future. The research shows that a lot of SPC-extensions are granted in the last couple of years, but (due to the fact that the product is still under protection) not 'effectuated' yet. Table 9 shows that especially in 2015 a lot of decisions on SPC-extensions are taken, which will materialize in the upcoming years.
- A final consideration is that the estimated size of the SPC-reward (i.e. the estimated economic value) does not always have a direct link to the 'efforts' (investments, R&D, etc.) the pharmaceutical companies made during the 2008-2014 period.[48] The SPC-reward is linked to a specific product, while efforts and investments of pharmaceutical companies are often spread over a broad portfolio of products, activities and investments.

3.3 The Orphan reward (article 37)

This section presents the results of the analysis of the orphan reward (Article 37). It is possible to grant 10 years of market exclusivity to new medicinal products which are designated as an orphan medicinal product. In line with Article 37 this 10-year period can be extended by two years[49] if the application for a marketing authorisation includes the results of all studies conducted in compliance with an agreed PIP[50]. This situation is summarised in the figure below.

Figure 18 Overview of the Orphan reward (market exclusivity)

[48] For this study, we used IMS Health data which covered this period. See Appendix C for more details.

[49] EC Regulation 1901/2006

[50] If an orphan product development falls in the scope of Article 7 or 8 of the Paediatric Regulation, a paediatric development is mandatory, unless a waiver is agreed.

Source: Frias, Z. EMA. Workshop for Micro, Small and Medium Sized Enterprises EMA. 26 April 2013. Data exclusivity, market protection and paediatric rewards. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf

Until mid-2016, four orphan-designated products have successfully fulfilled the requirements of article 37 of the Regulation, thereby becoming eligible for the specific reward.[51]

- Xagrid (Anagrelide) is a medicine for the reduction of the platelet count in patients at risk of essential thrombocythemia. Xagrid has been granted EU marketing authorisation in November 2004 and is currently reimbursed in eleven countries (see table below). The decision on the agreement of a PIP (required for the orphan reward) was taken in February 2014.[52]
- Tobi Podhaler (Tobramycin) is a suppressive treatment of chronic pulmonary infection in adults and children aged 6 years and older with cystic fibrosis. Tobi Podhaler has been given EU marketing authorisation in July 2011 and is reimbursed in eleven countries (see table below). The decision on the agreement of a PIP (required for the orphan reward) was taken in September 2014.[53]
- Kuvan (Sapropterin) is a treatment for phenylketonuria (PKU). EU marketing authorisation was granted in December 2008.[54] The product is currently available in eleven countries. The decision for the orphan reward was taken in July 2015.
- Soliris (Eculizumab) is medicine for the treatment of paroxysmal nocturnal hemoglobinuria. Soliris has been authorised in June 2007 and currently available in ten countries (see table below). The decision on the agreement of a PIP (required for the orphan reward) was taken in April 2016.[55]

Table 18 below shows an overview of the EU Member States that reimburse some of the products. In total, 16 EU Member States provide reimbursement. Only in four Member States all four products are reimbursed (Denmark, France, Luxemburg and the Netherlands).

Table 18 Overview of reimbursing countries for medicines with orphan reward

	BE	BG	CZ	DK	EE	EL	FI	FR	HU	LU	LV	NL	RO	SI	SK	SE
Xagrid	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓			✓
Tobi Podhaler		✓	✓	✓	✓		✓	✓		✓		✓		✓	✓	✓

[51] EMA, annual reports to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation. Another product is currently under assessment by the CHMP of EMA and may be authorised in 2016 (personal communication European Commission).

[52] EMA, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000720-PIP01-09-M02/pip_000411.jsp&mid=WC0b01ac058001d129.

[53] EMA, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000184-PIP01-08-M02/pip_000088.jsp&mid=WC0b01ac058001d129.

[54] EMA - Kuvan, EU/3/04/199. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000010.jsp&mid=WC0b01ac058001d12b.

[55] EMA, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000876-PIP05-15/pip_001430.jsp&mid=WC0b01ac058001d129.

	BE	BG	CZ	DK	EE	EL	FI	FR	HU	LU	LV	NL	RO	SI	SK	SE
Soliris	✓			✓		✓	✓	✓	✓	✓		✓	✓	✓		
Kuvan	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓			✓	

Based on market reports.

3.3.1 General market trends

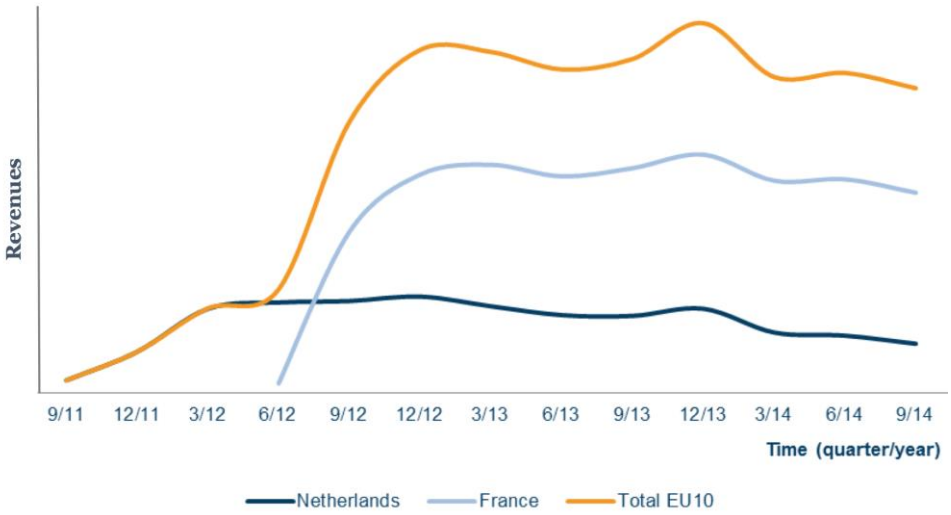
Compared to the IMS Health data available for the SPCs, the data available for these four products is limited in scope and 'quality'. This is mainly due to the fact that all four products are still under protection (no generic entry). This implies that our analysis of available data is also limited[56] and only shows some general market trends. See Appendix C for more details. Moreover, there is also limited data coverage over the different reimbursing countries. As a result, only the data for one product is presented.[57]

- Price development – For most of the countries, the price at the end date of our sample (Q3-2014) shows a relatively small decrease over time (up to 10%). This is for example the case in Bulgaria, the Czech Republic, Finland and the Netherlands. In Sweden, the price shows first a small increase, followed by a small decrease; specific details were not revealed.
- Revenue development – The data shows that, after the EU marketing authorisation (July 2011), there is a gradual increase over time in the revenues. This mainly results from the fact that the moment the product becomes available in a country (and is reimbursed) varies. In the Netherlands for example the sales start in the final quarter of 2011, while for France this is in the second quarter of 2012. The next figure shows the development in revenues for ten Member States over the period 2011-2014. France and the Netherlands represent the biggest share of the revenues.

[56] As described before: the IMS Health data available for this study covers the period 2008-2014. The last available data point is the 3rd quarter of 2014. The scope and limitations of the dataset are described in Appendix C.

[57] Due to restriction in the IMS Health license to present individual product data, the description of the market development is limited and does not reveal absolute values.

Figure 19 Development of revenues for an example drug



Based on IMS Health data. Note: the absolute revenue figures cannot be revealed for confidentiality reasons. Covered countries: Bulgaria, Czech Republic, Estonia, Finland, France, Luxembourg, Netherlands, Slovakia, Slovenia and Sweden. Note: the revenues include both adult and paediatric usage.

3.3.2 Economic value

Due to the fact that the four products are still under protection, it is not possible to estimate the economic value of the orphan reward. At the same time, a projection of the current data towards the moment of loss of exclusivity in the future is unreliable. This is mainly related to the data availability (see above) and the uncertainty about the effects of generic entry (ie, will there be generic entry? what will be the effect on the prices?). Nevertheless, the approach to estimate the economic value could be similar to the approach used for the calculation of the rewards from the SPC-extension, the main difference would be that the delay is two years (eight quarters) instead of two quarters.

In relation, Kreeftmeijer-Vegter et al. (2014) observed that after the Regulation came into force, it takes longer for a developer to obtain marketing authorisation for a paediatric medicine for rare diseases.[58] The exact causes of this phenomenon are not yet clear, but some have argued that it may be due to restrictive development conditions.[59] These barriers may have a negative impact on the 'popularity' of the reward. The interviews conducted within this study indicate that in some cases companies chose to withdraw the orphan designation following completion of the PIP and prior to obtaining marketing authorisation, in order to create the opportunity to benefit from the SPC prolongation (higher financial return). This choice varies per product and depends on the market circumstances (e.g. expected profit, expected generic entry, etc.).

[58] Kreeftmeijer-Vegter 2014 The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children. Orphanet J Rare Dis. 2014 Aug 5;9:120

[59] Shen 2014 New Financial and Research Models for Pediatric Orphan Drug Development - Focus on the NCATS TRND Program. Pharmaceut Med. 2014 Feb 1;28(1):1-6.

With regard to the situation in the US, we found some relevant literature on the economic value of the vouchers which are used. These insights are presented below. Please note that these insights cannot be directly compared with the EU.

- In the US, medicines for rare diseases (less than 200,000 people affected) benefit from an Orphan Drug Exclusivity (ODE) of 7 years, after approval of a New Drug Application (NDA) or a Biologics License Application (BLA).[60] Section 505(A) of the Modernization Act provides for a six-month period of marketing exclusivity as an incentive to industry to conduct studies requested by the FDA.[61] The applicant must fulfil the following conditions: be in receipt of a written request of FDA, submit study reports after receipt of the written request and meet the conditions of the written request. If this type of medicines is tested in children, with success, the six-month exclusivity add-on comes on top of the market exclusivity period of 7 years or patent protection period.[62] In the EU, the six-month SPC prolongation cannot be used in combination with the orphan exclusivity.
- The Rare Paediatric Disease Priority Review Programme (RP-PRV) of the FDA is another incentive that stimulates the development of medicines for rare paediatric diseases. If the disease affects human beings not older than 18 years and this disease is also included in the Orphan Drug act, the developer can get a Priority Review Voucher. This system was introduced in 2014[63] and can be used for any subsequent drug of the developer to expedite the review of a drug in their pipeline or the voucher can be sold to another company.[64] This system is summarised in the figure below.

Figure 20 Priority Review Voucher

[60] Orphan Drug Act and 21 CFR 316.31

[61] U.S. Food and Drug Administration (FDA) Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric "Rule," and their Interaction [Internet]. Accessed on: 25 March 2016. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm

[62] CDER Patents and exclusivity May 2015

[63] FDA. 2012. Safety and Innovation Act, Section 908 the "Rare Pediatric Disease Priority Review Voucher Incentive Program".

[64] Melissa S. Tassinari 2012 Pediatric Regulations 2012: Permanent Laws and New Provisions under FDASIA

Source: Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers. 2015. Online available at: http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA's-Priority-Review-Vouchers/.

The programme, however, is an experiment - once three vouchers are awarded (which is currently the case), the programme's efficacy and impact on the development of new drugs for rare paediatric diseases will need to be assessed by the Government Accountability Office (GAO) (2016). After the assessment, the Congress can make the programme permanent.[65]

It has been estimated that by using this voucher the review process could be shortened from 18 months (average) to 6 months.[66] The economic impact of this voucher is estimated at $US300m.[67] This is an indication of the economic impact, because it is not clear for which new medicine the voucher will be used. Each medicinal product serves a unique market and they are hard to compare. On December 31, 2015, there have been 11 requests for a RP-PRV. Of these, six requests have been granted, two have been denied and three are still under review.[68] Of the six awarded vouchers three have already been sold (see Table 19).

Table 19 Priority review vouchers granted under the RP-PRV[65, 69]

Year	Disease	Drug	Company	Sold
2014	Morquio A Syndrome	Vimizim (elosulfase alfa)	Biomarin	Sold for $67.5m
2015	High-risk neuroblastoma	Unituxin (dinutuximab)	United Therapeutics	Sold for $350m
2015	Rare bile acid synthesis disorders	Cholbam	Asklepion	Sold for $245m
2015	Hereditary orotic aciduria	Xuriden	Wellstat	-
2015	Hypophosphatasia	Strensiq (asfotase alfa)	Alexion	-
2015	Lysosomal acid lipase (LAL) deficiency	Kanuma (sebelipase alfa)	Alexion	-

Another approach to determine the economic value of this reward is to ask the pharmaceutical industry how much money they want to spend to buy a priority review voucher. Robertson et al. conducted a study on this subject and it appeared that pharmaceutical companies are willing to pay $US94m for a priority review voucher. The researchers also asked about how much holders of a voucher would expect to receive when selling it. On average, the holders would expect to receive $US188m.[70] Based on this information, it can be concluded that the impact of the

[65] The Business of orphan drugs is booming. Suzanne Shelley, Contributing Editor, August 26, 2015. Available from: http://pharmaceuticalcommerce.com/brand_communications?articleid=27627

[66] David B. Ridley. 2006. Developing Drugs For Developing Countries. Health Affairs 25, no. 2 (2006): 313–324

[67] David B. Ridley. 2010. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. Lancet 2010; 376: 922–27

[68] United States Government Accountability Office (GAO) 'Rare diseases: too early to gauge effectiveness of FDA's pediatric voucher program' March 2016 [Internet] Accessed on: 25 March 2016. Available at: http://www.gao.gov/assets/680/675544.pdf

[69] Priority Review Voucher 'Recipients' [Internet] Accessed on: 25 March 2016. Available at: http://priorityreviewvoucher.org/

[70] Robertson AS, Stefanakis R, Joseph D, Moree M (2012) The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development. PLoS Negl Trop Dis 6(8): e1750.

priority review voucher can be roughly estimated at hundreds of millions ($US), depending on the level of acceleration of the review process. As multiple requests for a RP-PRV have been made by the industry, GOA suggests that other incentives, such as the additional period of "market exclusivity" may be more effective to incentivise drug development than priority review vouchers (i.e., there is not yet any evidence that the programme has been effective in achieving its goal).[71]

3.4 The PUMA reward (article 38)

In this section, we present the assessment of the paediatric use market authorisation (PUMA) reward (article 38). The introduction of the PUMA reward served two main objectives. The first objective is to increase research on paediatric drugs, the second is to reduce off-label prescriptions of medicines to children. It appeared that the 'regular' market forces insufficiently stimulated relevant research aimed at the specific development and authorisations of paediatric medication. The main barriers relate to (i) costs and benefits, and (ii) the research and approval process. The costs of paediatric studies are, compared with the size of the potential market, often financially unprofitable for pharmaceutical companies. In addition, the design of clinical trials of paediatric medicine can be difficult (due to the small population size), while the approval process can take a long time.[72] In order to solve these issues, the PUMA reward was instigated by the European Commission, as a part of the Paediatric Regulation.

As described in section 3.1, the granted PUMA will provide the manufacturer with an 8-year period of data exclusivity. During this period, the marketing authorisation dossier of the PUMA cannot be used in support of an application, the latter needed to be substantiated by the results of pre-clinical tests and of clinical trials. Generic applications cannot be submitted during this period.[73] After these 8 years, there is an additional 2 years of market protection. During this period the generic product can be approved, but cannot be placed on the market. These 2 years of market protection can be extended with an additional year, when in the data exclusivity period an additional authorisation is acquired for one or more therapeutic indications which bring significant clinical benefit in comparison with existing therapies. Please note that the PUMA does not ensure market exclusivity. Other pharmaceutical companies will be able to conduct their own studies on the same product as the one of the originator company, and apply for a PUMA themselves.[74] A PUMA will only be granted when the medicines are intended solely for the use in children.[75]

In this section, we describe the actual use of the PUMA-reward, present some general market trends, discuss, to the extent possible, the economic value of the reward and assess a number

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[71] GAO. (2016). Rare Diseases. Too early to gauge effectiveness of FDA's Pediatric Voucher Program. Report to Congressional Committees. GAO-16-319. Available at: http://www.gao.gov/assets/680/675544.pdf

[72] Rocchi F., Paolucci P., Ceci A. & Rossi P. (2010) 'The European paediatric legislation: benefits and perspectives' *Italian Journal of Pediatrics* 36:56 P. 1-7.

[73] Hathaway, C. Manthei, J. and Schere, C. (2009) 'Exclusivity strategies in the United States and the European Union'. *Food and Drug Law Institute* Available at: https:/www.lw.com/upload/pubcontent/_pdf/pub2655_1.pdf.

[74] Permanand G., Mossialos E. & McKee M. (2007) 'The EU's new paediatric medicines legislation: serving children's need' *Archives of Diseases in Childhood* p. 808-811.

[75] Rocchi F., Paolucci P., Ceci A. & Rossi P. (2010) 'The European paediatric legislation: benefits and perspectives' *Italian Journal of Pediatrics* 36:56 P. 1-7.

of specific hypothesis from 2004. Because only two products received the PUMA-reward, the analysis of the available data is limited[76] and we are therefore only able to show some general market trends. See Appendix C for more details.

3.4.1 Actual use of the PUMA reward

Until now, two PUMAs have received a positive opinion from the EMA's Committee for Medicinal Products for Human use (CHMP).

On the 5th of September 2011, the first PUMA was granted to Buccolam (midazolam), for the treatment of prolonged, acute, convulsive seizures in paediatric patients from the age of 3 months to 18 years.[77] It was developed by Auralis, a specialized pharmaceutical company that developed technically complex products, in collaboration with Therakind (specialized paediatric drug development company). Auralis was acquired by ViroPharma in May 2010, so before the submission of the PUMA-reward.[78] The second PUMA was granted to Hemangiol (propranolol), from the company Pierre Fabre, for the treatment of proliferating infantile haemangioma on the 21st of February 2014.[79,80]

Both Buccolam and Hemangiol are reimbursed currently in 10 (different) countries. An overview of the status is provided in the next table. Reimbursement for Hemangiol is expected for the Czech Republic and Italy in the fourth quarter of 2015, as well as for Belgium (Q1 2016), Greece (Q3 2016) and Slovakia (Q4 2016).

*Table 20 Overview of reimbursing countries (and * planned) for medicines with PUMA reward*

Buccolam (midazolam)	**Hemangiol (propranolol)**
Denmark	Austria
Finland	Denmark
France	France
Germany	Germany

[76] As described before: the IMS Health data available for this study covers the period 2008-2014. The last available data point is the 3rd quarter of 2014. The scope (and limitations) of the dataset is described in Appendix C.

[77] EMA (European Medicines Agency) 'European Medicines Agency gives first positive opinion for paediatric-use marketing authorisation' *Press release 24-06-2011* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001287.jsp&mid=WC0b01ac058004d5c1.

[78] Watson J. & Nowacki K. (2015) 'The first paediatric use marketing authorisation: a case study' *Therapeutic Innovation & Regulatory Science* 49(2) p. 297-301

[79] EMA (European Medicines Agency) 'European Medicines Agency gives first positive opinion for paediatric-use marketing authorisation' *Press release 21-02-2014* Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/02/news_detail_002030.jsp&mid=WC0b01ac058004d5c1.

[80] Rani N., Budhwaar V. & Nanda A. (2015) 'A comprehensive study on the regulation of pediatrics in Us, Eu and India: present status and future prospective' *Advances in Chemistry and Biochemistry Sciences* 2 1 p. 1-12

Greece	the Netherlands
Ireland	Portugal
Italy	Romania
Spain	Slovenia
Sweden	Spain
UK	Sweden
	Czech Republic *
	Italy *
	Belgium *
	Greece *
	Slovakia *

Based on public market reports, e.g. http://www.londonstockexchange.com/exchange/news/market-news/market-news-detail/SHP/12060064.html

Within the context of this study, the EMA provided an overview of products (Table below) that relate to possible future PUMA requests (article 30 of the Paediatric Regulation).[81] This overview is only a subset of the number of PIP applications '*intended for future PUMA*'. An application is recorded as 'intended for future PUMA' if the developer is already the marketing authorisation holder.[82] The overview indicates for which medicines there has been a first PIP application (subsequent modification procedures are excluded from this overview). Some of these PIP applications completed in the past, resulted in an orphan reward under article 37 (Tobi Podhaler) or a PUMA-reward (Buccolam and Hemangiol). Several PIP applications in this overview have been completed, but there is no further information available if the developer applied for a PUMA-reward, SPC-extension or orphan-reward. Some PIPs will be completed later in 2016/2017 (e.g. budesonide).

[81] EMA 19-02-2016 'PIP applications for future PUMA'

[82] If this is not the case, it will be 'an application for marketing authorisation which is not authorised in the Community at the time of entry into force' and falls under article 7. This means that this application will be classified in a different way in the EMA databases.

Table 21 Overview of possible future PUMA requests (article 30)

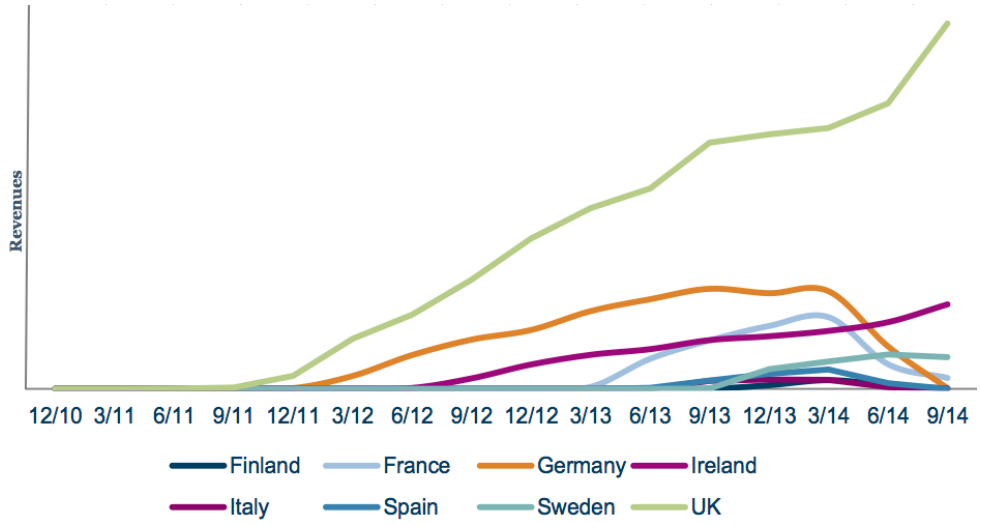
Substances	Application Number	Submission date	Name	Decision No.	Decision date
Influenza virus surface antigens	EMEA-000149-PIP01-07	08/02/2008	Decision published	P/40/2009	23/03/2009
Tobramycin	EMEA-000184-PIP02-14	14/03/2014	Decision published	P/0184/2014	06/08/2014
Glucose (monohydrate)	EMEA-000221-PIP01-08	04/04/2008	Decision published	P/45/2009	24/03/2009
Idursulfase	EMEA-000294-PIP02-12	08/10/2012	Decision published	P/0194/2013	29/08/2013
Midazolam (as the Hydrochloride salt)	EMEA-000395-PIP01-08	08/10/2008	Decision published	P/155/2009	11/08/2009
Human immunoglobulin	EMEA-000415-PIP01-08	07/11/2008	Decision published	P/165/2009	14/08/2009
Propiverine	EMEA-000502-PIP01-08	30/01/2009	Clock stop		00/00/0
Propranolol hydrochloride	EMEA-000511-PIP01-08	27/02/2009	Decision published	P/194/2009	07/10/2009
Levonorgestrel	EMEA-000606-PIP01-09	22/05/2009	Decision published	P/75/2010	05/05/2010
Ciprofloxacin	EMEA-000675-PIP01-09	14/08/2009	Clock stop		00/00/0
Fluconazole	EMEA-000676-PIP01-09	14/08/2009	Clock stop		00/00/0
Diclofenac sodium	EMEA-000879-PIP01-10	10/02/2010	Clock stop		00/00/0
Risperidone	EMEA-001034-PIP01-10	11/10/2010	Decision published	P/167/2011	06/07/2011
Budesonide	EMEA-001120-PIP01-10	13/12/2010	Decision published	P/0285/2011	30/11/2011
White soft paraffin / Liquid paraffin	EMEA-001789-PIP02-15	26/10/2015	Clock stop		00/00/0

3.4.2 General market trends

The PUMA reward for Buccolam (midazolam) was granted in September 2011 and for Hemangiol (propranolol) in February 2014. Due to the fact that the dataset available for the study ends in the third quarter of 2014, especially the data for Hemangiol is very limited. For Hemangiol data is only available for France (Q1-3 2014) and for Germany (Q3-2014).[83] See Appendix C for more details. As a result, only the data for Buccolam is presented here.[84]

- Price development – The data shows that in all available countries the price for Buccolam is fixed, from the moment of introduction to the end date of the sample. Between countries there exist substantial differences in the price level: up to 47% between the highest and the lowest price.
- Revenue development – After the PUMA-reward in September 2011, the revenues for Buccolam show a slow increase for the different countries. The strongest grow is recorded in the UK, while other countries show a much lower grow curve. The next figure shows the development in revenues for eight Member States over the period 2011-2014.

Figure 21 Development of revenues Buccolam



Based on IMS Health data. Note: the absolute revenue figures cannot be revealed for confidentiality reasons. It is not known why the revenues in Germany and France show a strong decrease again in the second and third quarter of 2014; (ii) data include both adult and paediatric usage.

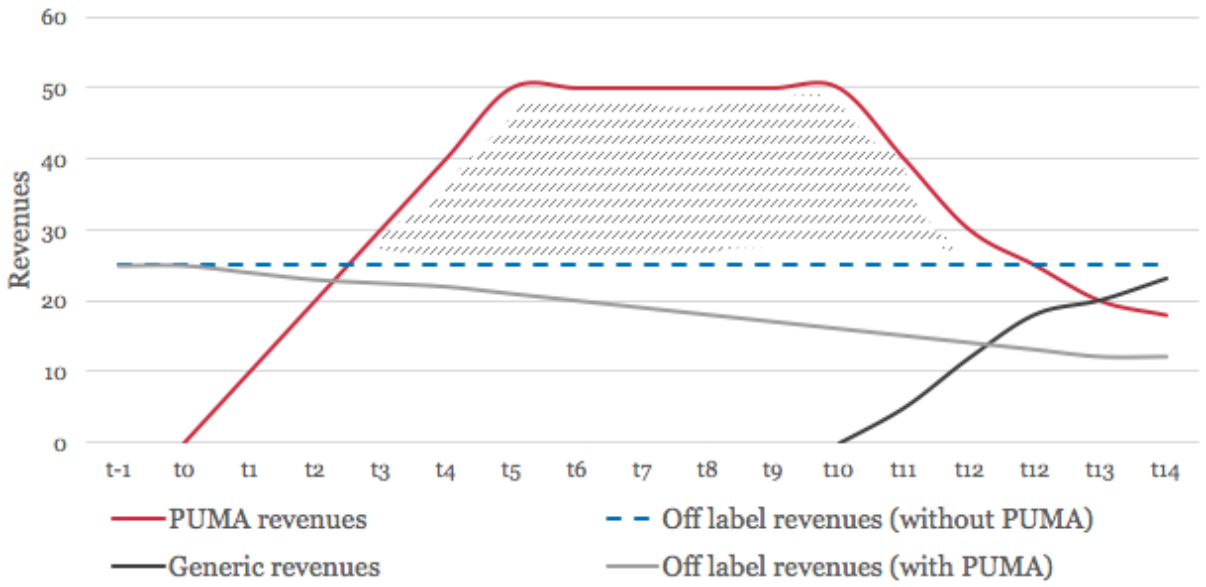
[83] France includes only hospital data; Germany includes hospital and retail data.

[84] Due to restriction in the IMS Health license to present individual product data, the description of the market development is limited and does not reveal absolute values.

3.4.3 Economic value

With regard to the assessment of the economic value of the PUMA-reward, the same principles can be applied as described in the presentation of the methodological framework. However, there is a fundamental difference: at the moment a PUMA-reward is granted the period of data exclusivity starts (instead of delayed as for the SPC-extension). This implies that the 'economic value' covers the 'monopoly benefits' a product receives from additional data exclusivity (8 years) and market protection (2 years). These benefits end at the moment this period of exclusivity ends and (maybe) generic products enter the market. This situation is presented in the figure below.

Figure 22 Assessment of the economic value of the PUMA reward



In the figure above, the light blue dotted line represents the off-label revenues which already exist in the market (and continues in a situation without the PUMA[85]). Currently, one PUMA is granted, the revenues for this product (red line) are expected to increase[86] and stabilise. Given the objective of the PUMA, we further assume that the level of off-label use/off-label revenue will reduce (grey line; although the extent to which is uncertain).[87] At the moment of the loss of exclusivity, it is expected that a generic product will enter the market (black line) and take over the revenues from the PUMA product. The shaded area between the PUMA revenues and the off-label revenues[88] represents the economic value of the PUMA-reward.

Given the current limitations of the available data, it is not possible to project the economic value of the PUMA reward. For Hemangiol we only have a few observations (one to three quarters for two countries). For Buccolam more observations are available, but still the

[85] In the figure, we suppose that the off-label use stays constant over time. In practice, off-label use may change.

[86] In the figure, we suppose that there are no revenues before the PUMA was granted.

[87] Interviews show that despite the presence of the PUMA-product, off-label use will most likely not disappear.

[88] Also without the PUMA product there would exist off label use. This can be seen as the counter factual situation.

projections are not reliable. It is uncertain at which level the currently increasing revenues will stabilise and what the impact of the loss of exclusivity will be. The relevant market dynamics are expected to be fundamentally different from (for example) the analysis of the SPC-extension.

3.4.4 Assessment of specific hypothesis

Within the context of this study a number of specific hypotheses were formulated which are assessed in the following sections. The hypotheses were:

- Hypothesis 1: PUMA incentives are too weak to make an actual change
- Hypothesis 2: PUMA is most likely to be effective where a child-specific formulation or dosage form is required (as this will lead to preferential prescribing over non-child-adapted products)
- Hypothesis 3: PUMA attracts mainly SMEs rather than bigger pharmaceutical companies
- Hypothesis 4: PUMA channels public R&D funds towards the most profitable areas of research, rather than into the development of medicinal products that are most needed among the paediatric population

3.4.4.1 Strength of the PUMA incentives

The RAND study[89] stated in 2004 that the PUMA incentive was likely to be relatively weak (in comparison to the SPC-extension). The main arguments for this statement were the limited scope of the data protection (limited to children), the limited market potential and lack of market exclusivity (see box below). The RAND study further concludes that there are concerns regarding the attractiveness of the PUMA and the impact on the producers of generic medicines. The incentive for data and market exclusivity are not effective for these off-patented products and the market opportunities seem to be insufficient in contrast to the economic risks for the development of these paediatric medicines (low return on investments).

With two positive opinions since the regulation came into force in 2007, it is clear that the pharmaceutical industry did not make full use of the PUMA, as was intended by the Regulation. This is also illustrated by the fact that the European Commission adapted its guideline by letting EMA accept PIPs for a PUMA that cover only certain age groups.[90]

The literature on the effectiveness of the PUMA is not extensive, but nevertheless confirms that the instrument is not very attractive. The Global Research in Paediatrics (GRIP) network indicated that the Paediatric Regulation as a whole has 'paved the way for paediatric development, but the PUMA concept is seen as unsuccessful.[91] The main reason for this is

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[89] RAND (2004), Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use.

[90] EMA (2014) 'European Medicines Agency gives second positive opinion for a paediatric-use market authorization: Hemangiol recommended for the treatment of proliferating infantile heamangioma' Press release EMA 21 February 2014. – Commission Guideline on the format and content of Paediatric Investigation Plans, Official Journal of the EU, 27.9.2014, C 338, p.1.

[91] GRIP (Global Research in Paediatrics) 'Public Consultation on Paediatric Report: the joint GRIP response' *European Union Seventh Framework Programme (FP7/2007-2013)26-11-2012 and* European Commission 'General report on experience acquired as a result of the application of the paediatric regulation (article 50(2) of regulation (EC) No 1901/2006) – 'Experience Acquired' and 'Lessons Learnt' (Sanco/D5/FS/(2012)1251190).

that the PUMA incentive does not protect the pharmaceutical formulations. In addition to this, health care professionals are allowed to prescribe other products (containing the same active substance) than the PUMA product off-label. The GRIP states that, 'unless there will be more valuable benefits provided in the future, it is unlikely that the PUMA will be more attractive in the coming years'. The PUMA should cover additional protection to cover the special paediatric dosages to create a significant incentive for the pharmaceutical companies. In this way, it prevents Member States to use off-label generic medicines. A simplified procedure for the PUMA might make it more attractive for pharmaceutical companies. The GRIP states further that academic networks are more interested in (re)developing off-patent products. With the instigation of the EU Seventh Framework Programme (FP7), which provides research funds from 2007-2013, scientific and clinical research will be stimulated. In a broader context, other authors suggest that especially the financial prospects are a limitation to license off-patent medicines for paediatric indications and that the target population for a PUMA is too small.[92] National reimbursement rules may not offer rewards that cover research costs for off patent medicines and investment sources for paediatric research among generic companies may be lacking. The interviews that were conducted confirmed that the attractiveness of the PUMA is limited, despite the fact that it can be interesting for individual companies (like in the case of Buccolam and Hemangiol). The main experienced barriers seem to be the uncertainty about the future benefits (small market, national regulation which may limit the revenues) in combination with other more attractive rewards such as the SPC-extension.

3.4.4.2 Effectiveness in relation to child-specific formulation or dosage

The next hypothesis is whether the PUMA is likely to be effective where a child-specific formulation or dosage form is required, as this may lead to preferential prescribing over non-child-adapted products.

The literature suggests that pharmaceutical companies seem to worry that market exclusivity will not prevent physicians by continuing to use competitor medicines off-label with the same active ingredient at lower costs. Substitution at the pharmacy level for cheaper, adult-form medicines might also take place.[93] Besides that, substitution practices of off-patent trademark medicines for generic medicines (or medicines that show similar therapeutic effect) is wide-spread among many of the European member states.[94] The use of non-child adapted medicines (off-label use of drugs), is extensive in hospital as well as outpatient care. Paediatric patients in hospital care are at risk of receiving at least one drug off-label. Almost all patients in neonatal hospital care are exposed to at least one medicine off-label.[95] This suggests that the most vulnerable paediatric group (neonates) has the highest exposure to the off-label use of drugs (and potential wrong doses), because there is no child-specific dosage form. In some countries like the UK, products can be introduced on the market without

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[92] Boon, W.P.C., et al. Improving the EU system for the market authorisation of medicines. Leiden: Escher, 2014.

[93] George B. & Tiwari J. (2014) 'A balance scorecard of the European Paediatric Regulation' International Journal of Pharmaceutical Sciences and Nanotechnology 7 (3) p.2529-2535.

[94] Mensonides-Harsema M.M. & Otte A. (2011) 'European regulatory framework on the use and development of pharmaceuticals and radiopharmaceuticals for pediatrics' *Hellenic Journal of Nuclear Medicine* p.43-48

[95] Kimland E. & Odlind V. (2012) 'Off-label drug use in pediatric patients' *Clinical Pharmacology & Therapeutics* 91 (5) p.796-801

market authorisation (e.g. hospital preparations). These products are always cheaper than authorised products. In the UK, hospitals often kept using medicines off-label for children. This was also the case for Buccolam, because the non-authorised product (used in hospitals) was cheaper.[96] A prohibition of unlicensed versions of comparable medicines which follow the PUMA procedure would be an enhancement to encourage further use of the PUMA procedure.[97] This is already the case in some European member states as for example Denmark. Based on these arguments we conclude that while this hypothesis is valid in theory, the day-to-day practice shows that the PUMA 'label' does not prevent physicians to prescribe non-child-adapted products.

3.4.4.3 Company size of PUMA applicants

With the introduction of the PUMA, it was expected that PUMA applicants were likely to be small and medium-sized enterprises (SME).[98] As described there are currently two PUMAs granted by the EMA. The first PUMA is granted to ViroPharma for Buccolam and the second to Pierre Fabre for Hemangiol. According to the strict definitions of the EC, both companies do not qualify as an SME[99] Nevertheless, the interviews conducted suggest (and confirm) that it is more attractive for SMEs to apply for a PUMA than bigger pharmaceutical companies. The main reason for this is the fact that this type of niche markets are often (first) served by small and specialized players. In the case of ViroPharma, the presence of the PUMA-reward was an interesting asset for Shire in the acquisition process.

3.4.4.4 Risk of diversion of public R&D funding

Finally, we assessed the risk that the PUMA may draw public R&D funds towards the most profitable areas of research, rather than into the development of medicinal products that are most needed among the paediatric population. The interviewees suggest that the risk exists, but is limited. This is highlighted by the small number of PUMA applications. According to Medicines for Europe, investments in some paediatric studies and specific paediatric indications (rewarded by the 6-month prolongation) are mostly driven by the commercial decision of a company. They suggest that pharmaceutical companies (engaged with the Paediatric Regulation) are steering into the direction of the profits and not in the direction of the needs. The PUMA does not provide sufficient measures and (financial) incentives to stimulate the research on existing medicines for paediatric use. This prevents pharmaceutical companies to engage in the PUMA procedure.

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[96] Information from interview.

[97] Watson J. & Nowacki K. (2015) 'The first paediatric use marketing authorisation: a case study' Therapeutic Innovation & Regulatory Science 49(2) p. 297-301.

[98] A SME has a staff headcount of which is lower than 250 persons, a turnover lower than €50m or a balance sheet total which is lower than €43m. See: Website European Commission: 'Growth, Internal Market, Industry, Entrepreneurship and SME's' Available at: http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition/index_en.htm.

[99] Financial information Pierre Fabre. Available at: http://www.evaluategroup.com/View/2737--co-coInfo/company/pierre_fabre. ViroPharma (Buccolam) is not a SME as the turnover and balance sheet total are higher than under the EC-definition. However, the number of employees for ViroPharma is lower than described under the definition above (<250 persons). Also Pierre Fabre Laboratories is not an SME, as the number of employees is much higher than described under the definition of the EC. Also, the turnover and balance sheet are higher than the EC definition.

4 Overall assessment of the rewards

This section provides the assessment of the rewards of the Regulation. This assessment is based on five specific evaluation criteria: (i) relevance, (ii) effectiveness, (iii) efficiency, (iv) coherence and (v) utility.[100] Before we discuss the different evaluation criteria, the objective of the Regulation and the assessed rewards should be clear.

The overall objective of the Regulation is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years. In the Regulation the following objectives are formulated.[101] These objectives are effectuated, amongst others, via the three described rewards.

- Facilitate the development and accessibility of medicinal products for use in the paediatric population
- Ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population
- Improve the information available on the use of medicinal products in the various paediatric populations.

In the next sections, we assess the Paediatric Regulation according to the evaluation criteria. We conclude with a brief section on potential improvements. The lessons learnt from the US Paediatric Regulation rewards are also taken into account.

The analysis is based on the results of a survey of pharmaceutical companies (Appendix A). 27 organisations responded to the open questions, of which 6 were SMEs and 1 was non-profit organisation, including 7 organisations conducting paediatric studies funded by FP7. The analysis of survey results is complemented by interviews with industry representatives and desk research.

4.1 Relevance of the rewards[102]

48% of the survey respondents state that the objectives of the rewards provided by the Regulation are relevant (relevant or highly relevant) to organisations' needs and objectives. Some respondents note that the reward incentivised organisations to sponsor and support the development of paediatric medicines, including in rare/orphan disease. However, at the same time, respondents claimed that as a result of the necessary additional costs involved with submitting PIPs, individual organisations may not be able to achieve a positive return on investment. The group of respondents that find the objectives of the rewards are only somewhat relevant share this view – the regulation may not lead to the capital allocation decisions that maximize value. Another concern is related to the delay in securing a reward in terms of data protection and patent extension. Reasons for which respondents argue that the

[100] See also the EC better regulation guidelines: http://ec.europa.eu/smart-regulation/guidelines/tool_42_en.htm.

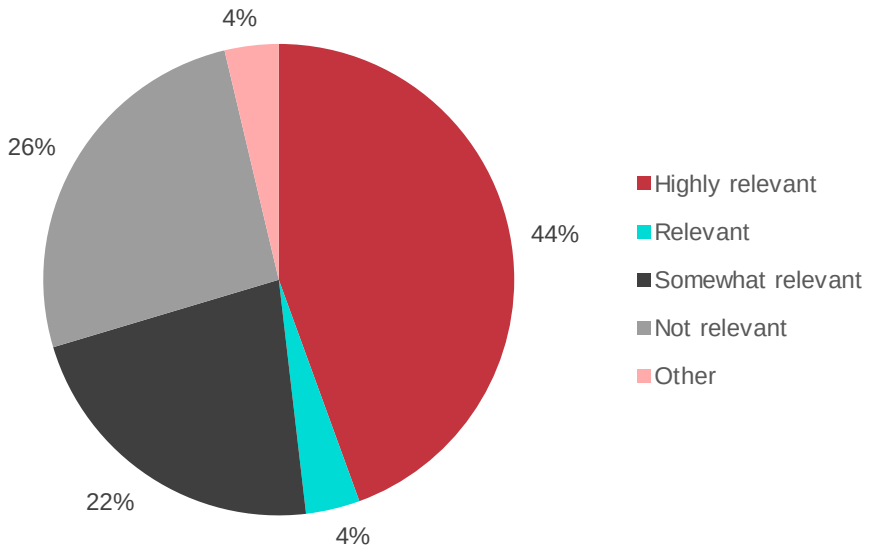
[101] Consideration 4 of the Paediatric Regulation. This consideration also mentions that: children will not be subjected to unnecessary trials or delaying the authorisation for adult medicines in achieving this overall objective.

[102] Relevance refers to the question whether the original objectives of the Regulation are still valid.

objectives of the rewards provided by the Regulation are not relevant to organisations' needs and objectives include the following:

- Organisations not extending an SPC or filing a PUMA;
- Lack of market for paediatric-only products in the paediatric population and therefore no opportunity to generate a significant income over a 6-month period;
- Concern over a mismatch between PDCO-required development of indications in therapeutics areas where the company has no expertise (in the development of paediatric indications) and/or needs to plan a separate development for children.

Figure 23 Are the objectives of the rewards provided by the Regulation relevant to your needs and objectives?



Source: Technopolis survey, based on 27 responses

4.2 Effectiveness[103]

Below we present the insights from the various sources on the overall effectiveness of the Regulation, including specific considerations towards the three rewards.

4.2.1 Overall effectiveness of the Rewards – insights from data and literature

Objective 1 - One of the explicit goals of the Regulation is to facilitate the development and accessibility of medicinal products for use in the paediatric population. Related to this is the objective to reduce the off-label use of medicinal products in the paediatric population. The paediatric investigation plan (PIP) and the related rewards (SPC-reward, but also the PUMA-reward) are the main tools to achieve this goal.

[103] Effectiveness relates to the question whether the Regulation has been successful in achieving (or progressing) towards the objectives mentioned above. See also: Ecorys, 'How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies', Final report, Ministry of Health, Welfare and Sport, 9 November 2015.

The previous sections have shown that especially the number of SPC-rewards show a large uptake over the period 2007-2015. For the orphan-reward and the PUMA-reward on the other hand the actual number of granted rewards is rather low (see sections 3.3-3.4). These mixed results raises questions especially about the effectiveness of the orphan and the PUMA-reward, but stress at the same time the relative attractiveness of the SPC-reward. The latter is in line with previous publications of for example by the EMA. In the report of the EMA on the experience acquired as a result of the application of the Paediatric Regulation (2012)[104], it is stated that 31 out of 152 new medicines have been centrally authorised for paediatric use since 2007.[105]. This number might increase in the future, because of new products in the pipeline and the completion of PIPs for which the conduct of paediatric studies has been deferred. In addition, a considerable number (72) of new paediatric indications were approved with regard to variations on authorised medicines and 26 new pharmaceutical forms were authorised for paediatric use.[106] Based on these observations, we conclude that the SCP-reward was effective and facilitated the development and accessibility of paediatric medicinal products. The Orphan-reward and the PUMA-reward were not deemed as effective.

Objective 2 - Regarding the objective to ensure ethical research of high quality, we noted that development of medicinal products for paediatric use is now an integral part of the business for the pharmaceutical sector and individual companies. Whether this qualifies as 'ethical research of high quality' cannot be judged based on the information sources we have. Nevertheless, the effect in 'volume' is visible. Recent information on the number of applications submitted for a PIP illustrates the (volume) effect of the rewards. By the end of 2015, in total, 858 PIP applications received an initial decision from the Paediatric Committee (PDCO) of the EMA. Based on data analysis from EudraCT, the proportion of paediatric trials as a percentage of all trials increased from around 7.5% (188 exclusively paediatric trials) in 2007 to 18.0% (473 exclusively paediatric trials) in 2015. The number of PIPs receiving positive opinion on compliance check (i.e., 'completed') was 99 by the end of 2015, and 116 PIPs by August 2016. As stated above (relevance), the relatively low number of completed PIPs is mainly due to the long development cycle of a medicinal product; this often takes more than 10 years. Since the Paediatric Regulation came into force, there has been limited progress in the paediatric oncology drug development. Unmet needs in paediatric oncology drug development are 'restricted increases in early phase paediatric oncology trials, regulatory pressure to propose early PIPs, lack of innovative trial designs and no new incentives to develop drugs against specific paediatric targets'.[107] Based on this we conclude that the rewards were effective in increasing the volume of paediatric research, but that it is not clear whether it classifies as 'ethical research of high quality'.

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[104] European Medicines Agency. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012. London: EMA, 2012.

[105] Of these, 10 met the conditions of the general authorisation requirements of Article 7 of the Regulation.

[106] European Commission. Report from the Commission to the European Parliament and the Council. Better Medicines for Children — From Concept to Reality General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use. COM(2013) 443 final. Brussels: European Commission, 2013.

[107] Vassal, G., Rousseau, R., Blanc, P., Moreno, L., Bode, G., Schwoch, S., ... & Saha, V. (2015). Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *European Journal of Cancer*, 51(2), p. 218-224.

Objective 3 - With regard to the objective to improve the information available on the use of medicinal products in the various paediatric populations, articles 45 and 46 of the Regulation apply. These Articles require that generated study data in the paediatric population must be submitted to national competent authorities to evaluate, for example, whether amendments are needed with regard to the Summary of Product Characteristics (SmPC). It appears, however, that not all SmPCs are updated. For example, in 2011, still one-third of (Estonian) children were exposed to prescription medicines not labelled for paediatric use.[108] Although there are paediatric medicines on-label, off-label use of prescription medicines still exists significantly in outpatient settings. For example, in the UK, products can be introduced on the market without market authorisation (e.g. hospital preparations). According to a stakeholder, hospitals will not stop using medicines off-label because the other comparable medicinal product is often more expensive (e.g. in the case of Buccolam).

Another measure that is relevant in this context is the European Network for Medicines Research at EMA (Enpr-EMA). This is a paediatric clinical research network, set up in 2009, to improve the quality of research of medicines in children. In addition, the EU provides funding to stimulate research in the field (Article 40) - i.e., research is ongoing targeting at least 25 off-patent medicines (active substances) with a total budget of more than €98m.[109,110] The PDCO has a crucial role in increasing high-quality research and promoting the development and authorisation of medicines for children.[111] For example, since 2008 approximately 18,000 paediatric study reports were published with information from the developer.

4.2.2 Overall effectiveness of the Regulation – insights from the survey and interviews

Three companies (out of 27 survey respondents) consider the regulation to be highly effective in achieving its objectives, stating that without the regulation, the organisation would not have committed to the development of paediatric medicine. It was noted that the effectiveness is higher for high-volume products and lower for indications with very limited patient numbers.

Interviewees provided a number of reasons to explain why, in their opinion, the Regulation has been effective. First, the Regulation has changed the priority given to paediatric development and has increased the amount of research and information available for the paediatric population. Second, the Regulation has been very effective in changing how companies approach paediatric research, conducting their research and incorporating the paediatric population in their development plans. However, it also (third point) created additional obligations and additional costs to bring new medicines to the market. Stakeholders indicate that the obligations have brought the biggest impact in terms of

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[108] Lass, J., Irs, A., Pisarev, H., Leinemann, T., & Lutsar, I. (2011). Off label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepidemiology and drug safety, 20(5). p. 474-481.

[109] European Medicines Agency. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. *EMA/428172/2012*. London: EMA, 2012.

[110] European Commission. Report from the Commission to the European Parliament and the Council. Better Medicines for Children — From Concept to Reality General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use. COM(2013) 443 final. *Brussels: European Commission*, 2013

[111] Dempsey E.M. & Connolly K. (2014) 'Who are the PDCO?' *European Journal of Pediatrics* 173 p. 233-235

increasing paediatric research and ultimately resulting in more medicines approved for children.

Interviewees also indicate that there are some difficulties in achieving the objectives of the rewards. The complexity of the regulatory environment and the process has increased, which is considered rigid by industry stakeholders. Furthermore, there is too much focus on regulatory compliance instead of facilitating product development. These compliance checks result in a delay in assessment. Interviewees report also fragmented administration and regulation: the interaction between the Paediatric Regulation and 'regular' pharmaceutical legislation is not optimal. Some of the requirements of the Regulation have been superseded by other regulations which might lead to double reporting. In addition to this, it is stated that the Regulation has met most of its objectives with combinations of incentives and obligations to promote research in paediatric indications and testing in children. Significant relevant data has been collected by companies from studies in children. Nevertheless, from a public perspective the effectiveness of the Regulation is somewhat reduced because some public services may decide not to pay for the registered paediatric medicines. There are multiple barriers on the national level which may hinder the introduction of paediatric medicines on the national level. A few national authorities indicated that the Regulation was set up from an overly narrow perspective, excluding affordability, cost-effectiveness and budget implications at the national level.

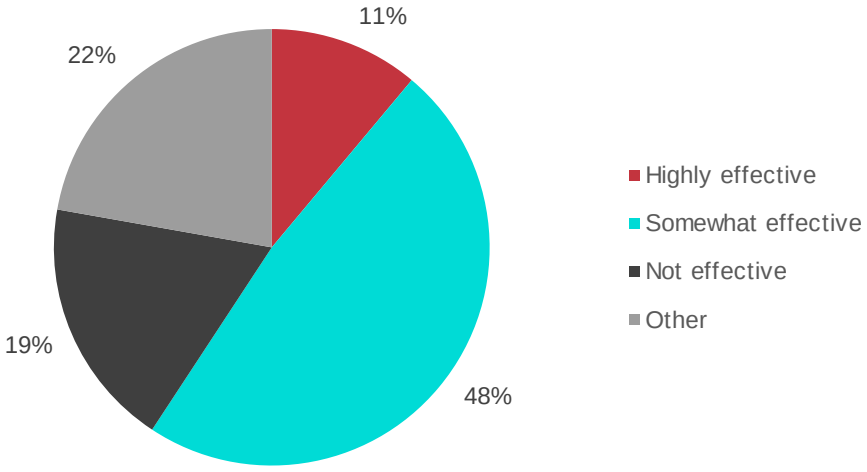
The survey respondents that state that the Regulation is somewhat effective or not effective argued that complications exist because reaching eligibility for rewards is difficult due to the following:

- PIP required very early in the product development, where uncertainties is significant and product discontinuity is likely;
- Paediatric subject recruitment difficulties;
- Potential imbalance between investment and reward;
- Study delays and additional time needed to conduct the necessary paediatric research and to complete the necessary regulatory approval procedures;
- Complexity of actually obtaining the reward once the research is completed in part in relation to:
  - Compliance check procedures
  - Type II variation assessed by CHMP (and not PDCO)
  - Necessity to submit the updated marketing authorisations from all 28 Member States (Article 36) with necessary translations (even if the SPC extension application is only to be made to a subset of Member States)
  - Variations of protocols by Local Regulatory Authorities and Ethics Committees and national patent offices, adding complexity and delay;
  - The deadline for SPC extension by national patent offices is 2 years prior to SPC expiry; the corresponding PIP and the associated regulatory procedures must have been fully completed by that time.
  - According to Art 36(3) of the Paediatric Regulation, in order to be able to apply for rewards the medicinal product must have been registered in all EU Member States

(MS). However, many non-centralised products are not approved in all MS for a variety of reasons.

Respondents also claimed that the proportion of PIPs that have been granted an SPC extension is relatively low. PUMA rewards are argued to not be effective because these do not take into account the pricing and reimbursement rules in some Member States. One respondent argued that the regulation generated a disadvantage to the organisation in the global market due to the delay the PIP imposed on market authorisation.

Figure 24 How effective are the rewards as a mechanism and means to achieve the objectives of the Paediatric Regulation?



Source: Technopolis survey, based on 27 responses

4.2.3 Specific considerations about the SPC reward

The Regulation linked to the SPC reward is an incentive for companies to develop medicinal products for use in children. For this purpose, companies need to agree a PIP before submitting marketing authorisation (rather than complete a PIP since completion may be deferred). There have been concerns raised by companies with regard to the PIP. According to the industry filing the PIP application takes significant time to complete because the applications are too broad. In addition to this, the requirements of the Regulation are perceived as stringent because the time limit to submit a PIP application is very early (end of clinical trial phase I) and the PIP application has to be overly detailed. The combination of these two issues makes it very hard for companies to engage in flexible product development. During the development phase of a medicine there is high uncertainty with regard to the benefit risk profile which may require adaptations of the study design. This makes it difficult for companies to complete a PIP without any modifications of the initially agreed programme. However, the EC and the EMA have mitigated this recently by clarifying in the new EC guideline and in the EMA procedural advice that filing the PIP application at the beginning or during phase II is acceptable. One stakeholder felt that there is a significant lack

of transparency during the process of assessment of SPC grants. The main reason for this is that there may be different procedures required for individual SPC extensions per country.

In addition to this, some stakeholders argued that the SPC extension results in a loss for society because generic entrance is blocked for 6 months. This six-month period is deemed very expensive in terms of paying the price for a branded product. This issue is described in more depth under 'efficiency'. Others indicate that society is obtaining the benefit of the clinical studies and the results of the studies and of the formulations for the paediatric population, regardless whether the product comes to the market or not. Developers of medicines indicate that the development costs are increasing, but the benefits of the potential SPC extension are reducing (compared to the costs). In particular, many compounds have more than one agreed PIP, nevertheless, companies can only secure reward for the non-orphan PIP that is attached to the first regulatory submission.

Overall the SPC reward is seen valuable by stakeholders and as a minimum incentive for the studies in paediatric population. There are however several factors which hinder the effectiveness of the SPC reward. For example, stakeholders indicate significant barrier at the level of the national health authorities in terms of timeliness of issuing updated marketing authorisations that contain the paediatric compliance statement. The process is also bureaucratic and labour intensive, especially for non-centrally approved products, when products are approved individually by the national MS health authorities.

Compared to the PUMA and the Orphan designation, the route to a potential SPC reward is considered obligatory according to stakeholders. With the PUMA and the Orphan designation, there is the option to choose to pursue various forms of product development for new products and relevant variations to existing products.

4.2.4 Specific considerations about the Orphan reward

Several interviewees indicate that the Orphan reward is not working well in view of the low number of orphan medicinal products that have obtained the reward since the instigation of the Paediatric Regulation. However, interviewees expect that there will be more relevant results in the future. One of the main reasons for the small amount of orphan designations is that the development of orphan drugs targeting children is complex and costly because the study population is very small. From a legal perspective, stakeholders stated that Article 37 is not clear because it concerns marketing authorisation. When the Regulation came into force, there were already several orphan products on the market (Orphan Regulation 2000). If these products were developed further for a new indication targeting children, this is not covered by Article 37 of the Paediatric Regulation because this Article is only focussing on the development of new products.

The difficulty to draft a PIP application for rare diseases has also been described in the literature (Kreeftmeijer-Vegter et al, 2014), focussing on orphan medicines. These authors concluded that the Regulation "added complexity to the research and development and regulatory process of orphan medicinal products, exemplified by the applicant's investment time and effort in drafting a PIP application". This complexity has led to a minor impact on

the availability of orphan drugs for children and has increased time to marketing authorisation.[112]

In addition, the therapeutic areas covered by research in children are currently reflecting more clearly the needs of adults instead of those of children, although research in children younger than 2 years seems to be increasing.[113] The proportion of clinical trials of all trials (adults and children) has increased over the last years (7.4% in 2008, 10.4% in 2012 and 12.4% in 2014). However, note that over time the number of adult clinical trials decreased while the number of paediatric clinical trials increased.[116]

Interviewees indicate that the two additional years can be very valuable for an orphan product when a company has invested in the development. However, they also indicate there is a drawback in the Regulation because it is not permitting a company to choose between the 2-year extension to orphan exclusivity or the 6-month SPC extension available for other, non-orphan products. The orphan reward may also bring other important incentives in the market place. This might be pricing and reimbursement advantages or positive acceptance and recognition of clinicians and stakeholders for an orphan drug, which may contribute to the effectiveness of the Regulation.

According to other interviewees, the orphan designation is one of the strongest incentives. However, in some cases where the substance is also registered for non-orphan indication the value of the patent extension may be greater than that of the additional exclusivity depending on the life cycle of the drug.

4.2.5 Specific considerations about the PUMA-reward

Until now two PUMA applications have been granted. It appears that there is no significant interest from product developers and academic networks for this award. The main reason for this is that the costs outweigh the potential revenue/profit as the return on investments in developing paediatric drugs is lower (or uncertain) compared to the development of adult drugs.

According to the interviewees, the investment in clinical trials for paediatric use is practically impossible in view of the high costs of studies and very low and unpredictable return on investments for new paediatric medicinal products. This makes it difficult for the PUMA to be a strong incentive. According to stakeholders, there are various reasons why the PUMA does not provide effective exclusivity. The main reason is that there might already be generics in the market because medicines are no longer protected by patents/SPCs or Orphan market exclusivity. This protection relates to the paediatric data/indication only and therefore restrains generic applications for that particular indication and their reliance on that particular data only. It is difficult to ensure that generics are not used for that protected indication when they are available on the market in some kind of pharmaceutical dosage form, for a different indication (off-label use/compounding).

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[112] Kreeftmeijer-Vegter, A.R., de Boer, A., van der Vlugt-Meijer, RH, de Vries, P.J. The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children. Orphanet Journal of Rare Diseases; 2014 (9):120.

[113] European Commission. Report from the Commission to the European Parliament and the Council. Better Medicines for Children — From Concept to Reality General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use. COM(2013) 443 final. Brussels: European Commission, 2013.

One of the interviewees indicates that the main reason to ask for a PUMA was for the administrative protection of the data. In addition to this, without the PUMA there would be no access to certain price procedures and it was financially attractive. Barriers for companies to use the PUMA includes off-label competition by generics and compounding and the high investment costs of clinical development. There is no certainty about the level of reward a company will ultimately get considering the price and volume of the product sold.

According to interviewees, applying for a PUMA is an overly rigid process because there needs to be absolute compliance. There is no possibility to explain little deviation from the opinion. From a public stakeholders' perspective it represents a risk that a company might increase the price of a product when it is introduced as a registered product. Overall, the PUMA reward is therefore not sufficient and effective in its current form to achieve the objectives it was intended to do. The PUMA reward could be more effective with incentives linked to easier route for pricing and reimbursement.

4.3 Efficiency

Efficiency (or inefficiency) normally relates to the relationship between the resources used by an intervention (like the rewards of the Regulation) and the changes generated by the intervention (e.g. more research and more approved paediatric medicines). This relationship is assessed in more detail in Chapter 2 (costs) and Chapters 5-6 (costs and benefits). Here, the focus is on the aspects of 'attractiveness' of the reward, as most stakeholders refer to it.

4.3.1 Insights from literature

EMA reported that the objectives of the Regulation could be achieved more efficiently, especially "the agreement and conduct of studies in PIPs, requiring feasible studies with children, identifying priority medicines for use in children, progressing regulatory science on paediatric medicine development, decreasing administrative burden by decreasing the number of minor changes to agreed PIPs".[114] This has been addressed through the change of the Commission guideline in 2014, through establishing a more streamlined process and by introducing the concept of (mandatory) "key binding elements" of a PIP.[115] Nowadays, a PIP only needs to be modified, if the company believes that one of these key binding elements should be changed. This substantially reduces the risk of PIP modifications for "minor" changes.

Because of the strict PIP requirements, pharmaceutical companies need to invest considerable amounts of time and resources to develop and execute the PIPs. Since the outcome of this process is less than certain, this makes paediatric drug

[114] European Medicines Agency. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012. London: EMA, 2012.

[115] European Medicines Agency (EMA) 'Paediatric investigation plans' [Internet] Accessed on: 25 March 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000608.jsp&mid=WC0b01ac0580925b1b

development relatively unattractive for small companies, such as biotechnology companies and start-ups.[116]

Also, mainly large pharmaceutical companies ('blockbuster' drugs) have benefited so far from the SPC extension. The orphan drug reward and the PUMA reward have been awarded to a total of six products only. Especially, the PUMA is felt to be inefficient by stakeholders, as also stated in the EC report Better medicines for children.[117] The PUMA appears not to be an attractive incentive for companies and SMEs to develop or repurpose already marketed drugs. Another reason for the relatively low number of PUMA rewards is the niche market in which the pharmaceutical companies have to operate. This creates uncertainty. Generic companies face a similar problem. It is considered relatively too costly to conduct clinical trials in a niche market.

Although generic companies are supportive of the Regulation, they have the opinion that the 6-month SPC prolongation is not efficient, because it is not addressing the therapeutic fields with the highest unmet needs. Overall, the incentives work better for new medicines still under patent protection.

4.3.2 Insights from stakeholders

There is consensus amongst survey respondents that the 6-month extension to SPC that can be granted as a reward for completion of required paediatric studies is the most attractive. The SPC reward is seen as 'valuable' for the completion of an agreed PIP and the associated regulatory procedures, are seen as more efficient. However, the procedure towards an SPC reward is overly complex. The (long) time needed to conduct the necessary paediatric research and the fact that only one SPC may be extended under the Regulation, results in difficulties. Other complexities/difficulties around the SPC reward are:

- Difficulties in extending the SPC in EEA countries like Norway and Iceland, although they benefit from all the research conducted
- Difficulties on the national level with the different patent offices
- For some products the SPC lasts longer than the orphan reward and a company cannot choose between these two rewards.

It is indicated by stakeholders that the orphan designation reward is also efficient. The two-year extension of market protection period in case of orphan drugs is seen as valuable, although only four orphan rewards have been granted to date. According to stakeholders the reward provides a return on investment for developing paediatric formulation and obtaining more specific data in children. Most of the orphan drugs do not have an SPC, so market exclusivity extension is important. In some cases, companies may not receive any reward after completing the PIP because the OMP status is not retained. Stakeholders indicate that there are also difficulties with not being able to choose between the rewards and not having the assurance that the reward is received after complying with the regulation.

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[116] Vassal, G., Rousseau, R., Blanc, P., Moreno, L., Bode, G., Schwoch, S. & Saha, V. (2015). Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. European Journal of Cancer, 51(2), p. 218-224.

[117] European Commission (2013) 'Better medicines for children from concept to reality' COM (2013) 443 FINAL

According to stakeholders the PUMA reward is the least efficient because it does not offer meaningful market exclusivity. A PUMA is granted to off-patent products which are already subject to generic competition. Despite the intention of an innovative company to invest in the preparation and the conduct of a PIP and associated regulatory procedures, the resulting PUMA is not likely to provide any commercial value. In addition to this, generic products will in many cases (continue to) be prescribed off-label for the newly authorised paediatric indication. Market access for a PUMA product is often a problem in addition to off-label use. One stakeholder noted that a company may conduct all relevant research, create new paediatric formulation, and register the product for reimbursement. But this registered product is often not prescribed by doctors in European countries because there is a cheaper alternative (compound).

Overall, the assessment shows that especially the SPC-reward is an (attractive) instrument that drives companies to carry out more research on paediatric medicines. For the orphan and PUMA-reward, the incentive is much smaller and pharmaceutical companies often do perceive these rewards as inefficient (or unattractive).

4.4 Assessment of the coherence[118]

The assessment of coherence focuses on whether there are overlaps/complementarities between the rewards and related EU or Member State action. In Table 22 we describe initiatives and rewards which are instigated by several EU member states.[119] This information is derived from the annual reports published by the EMA from 2012-2014.[120] Most of the initiatives and benefits are complementary and there appears to be some overlap – see also Table 22. For example, with regard to facilitating the development and accessibility of medicinal products for use in the paediatric population, we encountered countries that focus on prioritised reviews of the clinical trials and data for paediatric medicines (Austria, Poland and Spain). Prioritising certain research might facilitate the accessibility of paediatric medicinal products in a way that these medicines will be faster on the market. Second, some EU member states like the United Kingdom and France are providing national legislation to diminish the off-label use of medicines for children, aimed at facilitating the development of paediatric medicines. In the UK, the Pharmaceutical Price Regulation Scheme (PPRS) provides financial incentives to encourage the use of paediatric medicines (initiated in 2014).[121] In France, a legal framework was introduced to regulate and reduce the use of off-label medicines in combination with a legislation to supervise the prescription of medicines for indications for which the medicines are not licensed (initiated in 2013).[122] In Italy, physicians are allowed to prescribe certain non-authorised medicines when they are included in an official list defined by the Technical Committee of AIFA (Law 648/96). These medicines are then reimbursed by the Italian NHS. However, this approach allows for more off-label

[118] The evaluation of coherence involves looking at a how well or not different actions work together.

[119] European Medicines Agency (2012-2014) 'Annual Report to the European Commission'

[120] The annual EMA reports on rewards and benefits include a section on MS rewards/incentives:

http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm

[121] Website UK Government (2014) 'Guidance Pharmaceutical Regulation Scheme 2014' [Internet]. Accessed on 25 March 2016. Available at: https://www.gov.uk/government/publications/pharmaceutical-price-regulation-scheme-2014

[122] Website Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) [Internet]. Accessed on: 25 March 2016. Available at: http://ansm.sante.fr/

use of medicines in children.[123] In Spain, prices for paediatric medicines are excluded from the reference pricing system and individually priced. The national initiatives might support the Paediatric Regulation in its implementation across the EU.

Research networks are also financially supported by countries to stimulate paediatric research. In the United Kingdom, the Medicines for Children Network has been initiated, specifically focussing on the development of medicines for children. In Austria, a research platform for paediatric research was created for the academia and the industry to stimulate cooperation in the development of paediatric medicines. These research networks provide a platform for paediatricians to pool their experiences and, in this way, improve the information available on the use of medicinal products and the best treatments available for children.[124]

In the area of paediatric (academic and hospital) research there are a number of large consortia which are involved in product development projects. Several organisations support this paediatric research by stimulating international cooperation and connecting existing networks. Examples of these organisations are European Society of Development for Pharmacology and the European Network of Paediatric Networks. In the Netherlands, a consortium with the industry has been created. In addition to this, the Netherlands was planning to build a research infrastructure (with support from the Ministry of Health) for medicines research for children. However, an adult structure has finally been set up in cooperation with the industry.

[123] Prada, M., Bertozzi C., Proietti B., Urbinati D., Intexo, IMS Health, The Italian 648/96 list: Approvals, rejections and methoid in AIFA's evaluation process between January 2013 and October 2015. ISPOR Scientific Presentation. Available at: http://www.intexo.it/wp-content/uploads/2016/07/2015-ISPOR-648-Law.pdf

[124] Website O.K.ids. Available at: http://www.okids-net.at/kinder-familie. Accessed on: 2-3-2016

Table 22 National incentives and benefits EU Member States

Country	National incentives and benefits		
Austria	Prioritised review of clinical trial applications. Clinical trial applications are immediately screened by an assessor. A prioritized scientific review is performed, if necessary.	Priority setting	2012
Austria	Consortium to implement a platform for paediatric research for both academia and industry. http://www.okids-net.at/	Research Network	2014
Italy	Reimbursement of medicines: several medicines have been included in a list according to Italian Law 648. These medicines are not licensed in Italy for specific paediatric indications. However, Law 648 allows physicians to prescribe medicines where no therapeutic alternatives are available (including for paediatric patients, in specific therapeutic indications, and after having received a positive opinion from the Italian Medicine Agency's Commissione Tecnico Scientifica). After this the medicine will be reimbursed by the National Health System. Law 648 is applicable on off-label indications for products specifically marketed in Italy, or for products which are not (yet) marketed in Italy. It is important to notice here that the inclusion of a medicine in the list of Law 648 does not modify the SmPC and therefore, the paediatric indications of these 'listed' medicines remain unauthorised and not extendable to other Member States.	Reimbursement	2012
Spain	Special measures for pricing of paediatric medicines. Pharmaceutical forms specifically intended for the treatment of paediatric population are excluded from the system of prices of references (Royal Decree 16/2012)	Pricing	2012
Slovenia	Fee waiver for clinical trials with the paediatric population	Incentive	2012
France	The introduction of a new legal framework with the aim to reduce and regulate the use of off-label medicines was implemented in combination with a related decree for 'Temporary Recommendations for Use'. This legislation was provided as 'a regulatory process for temporarily supervising the prescribing of medicines for indications for which they are not licensed'. This legislation applies to any medicinal product and may therefore have an impact on the use of medicines in children for which off-label prescription is frequent. At the moment of publishing the 2013 annual report of the EMA, it was too early to assess the impact of this new legislation in paediatrics.	Regulation	2013
Poland	Priority review of paediatric data decided on a case-by-case basis	Priority setting	2013
Spain	Paediatrics and perinatal medicines are considered priorities (by "Instituto de Salud Carlos III", decision on 11th of June 2013). The legislation was instigated to fund strategic health actions as part of a state programme for investigation of social objectives.	Priority setting	2013
United Kingdom	Medicines for Children Research Network. The UK Government provides support for the NIHR Medicines for Children Network (MCRN). This network provides infrastructure across all of England to support the delivery of paediatric medicines studies (although not direct funding). http://www.mcrn.org.uk/	Research Network	2013

United Kingdom	Financial incentives to encourage use of paediatric medicines including PUMA. The Pharmaceutical Price Regulation Scheme (PPRS) is a mechanism used by the UK Department of Health to control the prices of branded prescription medicines supplied to the NHS by regulating the profits that companies can make on their NHS sales. This is an incentive in a way that it provides support for research and development (R&D) through allowing R&D in the assessment of a company's profitability of its business with the NHS.	Regulation	2014

4.5 Assessment of the utility[125] and potential for improvement

In terms of the number of medicines that has become available, there is already a visible positive impact.[126] However, the impact of the regulation on research quantity and quality in children stemming from PIPs is not yet clear.[127] Funding is an important aspect to support the development of paediatric medicines. Expanding funding options for research into paediatric medicines, e.g. via 'Horizon 2020' or other relevant EU Research funds (e.g. Innovative Medicine Initiative) might provide (also for companies) a framework for investment in paediatric research.[128]

4.5.1 View of Medicines for Europe

According to Medicines for Europe, several measures could be taken to improve the effects of the Paediatric Regulation. At this moment, it is possible for multiple stakeholders to receive the six-month extension. Medicines for Europe would like to be ensured that the SPC prolongation should be awarded only to the market authorisation holder and just for one SPC. It has to be excluded that certificates, which are granted to third parties, will receive 6-month SPC prolongations too. This means that the SPC reward should be granted exclusively to the company who sponsors the paediatric studies and is responsible for the compliance with the PIP.

A second (legal) improvement of the six-month SPC prolongation proposed by Medicines for Europe is to remove the possibility of "negative term SPCs". When a market authorisation procedure for a product takes more than 5 years after filing for a patent, than the SPC will extend the patent protection for that certain product over the 5 years. However, if this period to obtain market authorisation takes less than five years, the formula gives a negative term:

Term = ([date of 1st MA in the EEA] – [date of filing of corresponding patent]) – 5 years

The market authorisation procedure for paediatric medicines often takes longer compared to the procedure for comparable products in adult use.[129] The Regulation therefore should govern whether or not an applicant is able to obtain SPC protection. By permitting the

[125] Utility: to what extent do the changes/effects of an intervention satisfy (or not) stakeholders' needs?

[126] European Medicines Agency. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012. London: EMA, 2012.

[127] Kreeftmeijer-Vegter, A.R., de Boer, A., van der Vlugt-Meijer, RH, de Vries, P.J. The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children, Orphanet Journal of Rare Diseases; 2014 (9):120

[128] Ruggieri, L., Giannuzzi, V., Baiardi, P., Bonifazi, F., Davies, E. H., Giaquinto, C., ... & Rabe, H. (2015). Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. European journal of pediatrics, 174(4),p. 481-491.

[129] Forresters, December 2011 'The CJEU allows negative term SPCs'

granting of negative term SPCs, the Court of Justice of the EU has reduced the time frame from 5 years to 4 years and 6 months from the filing of a patent before SPC protection becomes a possibility. In this situation, companies will benefit from the paediatric extension of their SPC and might gain more profits out of the SPC prolongation. Only an amendment of the SPC Regulation (amending Article 13, Regulation 469/2009) could change this situation.

The transparency around the SPC procedure could also be improved, according to Medicines for Europe. However, measures on Member State level are needed to achieve this, through national legislation and within the IP offices governed by a different legislative regime. In addition, incomplete PIP applications, missing data in the PIP applications, should not be tolerated by EMA.

The effect of the PUMA reward could be improved by taking into account various practical aspects, for example legal and payer aspects.

In the past, there have been several withdrawals from the orphan designation procedure. According to the Medicines for Europe, the reason for this is that it is not possible to receive the Orphan designation for both an orphan and a non-orphan designation. This makes a SPC more valuable for pharmaceutical companies compared to an orphan designation, also because there are potentially more benefits in the SPC reward. When a product has an orphan designation, the product cannot receive a SPC extension, even if these products have SPC pending. There are currently court cases regarding the SPCs. In some countries, patent offices receive specific training about the SPC procedure under the national regulatory system (e.g. the Netherlands). As a result, there is more flexibility in the way these patent offices deal with SPC submission from companies.

4.5.2 View of other stakeholders

Based on the interviews with stakeholders and the survey to industry, a number of potential improvements have been listed to enhance the positive effects of the rewards.

Suggestions to reduce cost via a revision of the PIP process include the following:

- Streamline the PIP modification process
- Split PIP requirements in short term objectives which are more manageable to achieve before patent expiry and granting the reward, and long term commitments to be fulfilled
- Adopt a more flexible approach with a 'full' PIP in case of new and innovative drugs, and a different (lighter) approach for Article 30 (off-patent) drugs
- Improve guidance on PUMA in relation to orphan drug submissions
- Continue and increase inter-agency collaboration to facilitate global paediatric programs
- Increase transparency, share best practice and paediatric experience and publishing aggregate data for those products that achieve the exclusivity incentive
- Revise Article 8 - Article 8 was intended as a bridging step when the Regulation was adopted, to ensure products already on the market would be developed further for children. According to the interviewees, this transition period is over, as all products that were on the market at the time of the adoption of the Regulation are now off-patent. This calls for the elimination of Article 8 for products that were already subject to Article 7, allowing future PIPs for the same product to be exempted.

Suggestions to reduce cost via simplification and revision of PIP authorisation process are the following:

- Committees could match protocol and endpoint designs more appropriately to common care practices in order to develop trials that can be executed in member countries.
- Revise the current form of Article 36(3) and allow the SPC extension also when not all Member States have approved the product.
- Base reward decisions on a positive compliance check (only)
- Centralise SPC extensions in Europe
- Harmonise advice and requirements across interested Institutions (PDCO, CHMP and EC) through enhanced internal coordination (for example as in the FDA). Applicants currently need to engage with advice from different bodies and this unnecessarily complicates the process. The different entities could also share their opinion at the time the company works with the PDCO (e.g. requests by the PDCO will be accounted for in the procedural part for the registration).
- Harmonise national processes - More measures regarding pricing and reimbursement at the national level could be taken by national authorities. In addition, a more streamlined process with the patent offices is preferred to remove barriers at the national level.

Suggestions to increase the incentive are the following:

- Introduce an extension of regulatory data protection for products not patent/SPC protected
- Revise the deadline for the extension applications taking into account the length of the PIP completion and the completion of the associated regulatory procedures
- Make the six-month extension of protection applicable to all types of protection (not just an SPC)
- Extend the period of market protection, rather than SPC extension
- Link the value of the rewards to the medical need in children and the real development cost
- Allow sponsors to choose between a prolongation of data exclusivity or of patent protection according to their situation. For some products, the SPC reward lasts longer than the orphan exclusivity. Allow the sponsor to choose the kind of reward that is the most valuable for a particular product. For non-protected orphan products there are cases where market exclusivity extension instead of the PUMA route would be preferable
- Allow the possibility of getting the SPC extension even with delayed paediatric drug development
- Increase the period of SPC protection
- Apply SPC extension to “any compound on patent” that is held by the company
- Create incentives for further voluntary PIP
- Create a level-playing-field and extend the Regulation to Iceland and Norway (EEA). The regulation has not yet been fully implemented in those markets; these countries benefit from the inclusion of the paediatric studies data into the approved products’ SmPC

(because they are part of the EU medicines regulatory system), but they do not grant the corresponding reward

- Enforce the regulation at the national level and eg eradicate the use of state substitution of unlicensed medicines or off-label use after a PUMA has been approved.

4.5.3 Potential for improvement – Lessons to be learned from the US

Before the introduction of the Paediatric Regulation in Europe, the EU has lagged behind the United States in issues concerning paediatric drug formulations.[130] The table below provides a brief overview of the development of US paediatric legislation.[131]

Table 23 US Paediatric Regulation

1994	1997	2002	2003	2007
• Paediatric Labelling Rule	• Paediatric Rule • FDAMA: Food and Drug Administration Modernization Act	• BPCA: Best Pharmaceutical For Children Act	• PREA: Paediatric Research Equity Act	• FDAAA: Food and Drug Administration Amendments Act

The current legislation stems from 2007 and includes a six-month patent extension for paediatric medicines in exchange for new data generated by adequate paediatric trials. An important contrast between the EU and the US Paediatric Regulation concerns the timeframe of the development plan. The PIPs (EU) need to be agreed at the end of Phase I, while the Paediatric Study Plans (PSPs) in the US need to be agreed at the end of Phase II. The incentives differ as there are differences in statutes and regulations that govern paediatric drug development.[132]

Another difference concerns funding of research for medicines in children. The funding of research provided by the EU (FP7 paediatric projects) is limited compared to a similar funding programme set up in the US (Paediatric Trials Network). In this programme paediatric clinical trials were funded with a 3 to 4 times higher rate compared to European studies.[133] Another difference is the fact that the amount of researchers from academic or public research institutions involved in paediatric research is relatively low in Europe. However, in the US creation of paediatric research networks are not mandated via the Regulation. Also, a difference is that the US legislation was designed to generate additional paediatric data and balances between mandatory requirements and voluntary incentives.

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[130] Breitkreutz J. (2008) 'European perspectives on paediatric formulations' Commentary *Clinical Therapeutics* 30:11 p. 2146-2154

[131] Zisowsky J, Krause A, Dingemanse J. Drug development of pediatric populations: regulatory aspects. Pharmaceutics 2010; 2: 364-388. Review.

[132] Ecorys Nederland B.V. 'How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies', Rotterdam: November 2015.

[133] Ruggieri, L., Giannuzzi, V., Baiardi, P., Bonifazi, F., Davies, E. H., Giaquinto, C., ... & Rabe, H. (2015). Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. *European journal of pediatrics*, 174(4),p. 481-491.

When new data is generated by adequate paediatric clinical trials, the voluntary US legislation offers patent prolongation in exchange. This in contrast with the EU legislation which was designed to mandate full registration of all new drugs for children, whenever there is a potential of paediatric use.[134]

Company efforts seem to be more encouraged and awarded in the US than in the EU (e.g. 6-month prolongation as a reward for ''voluntary engagement' in paediatric studies). In the EU, companies need to comply with additional requirements. Authors have suggested to coordinate European and US PIPs in order to avoid duplication and to accelerate development in for example specific (cancer) diagnoses.[135] Benefits under the US legislation can be categorised as:

- The economic value of improved paediatric health outcomes from greater access to medicines (better label information from appropriate studies of paediatric pharmacotherapy);
- The value of the pharmaceutical innovation stimulated by the 6-month market exclusivity provision.[136]

[134] Rose K. (2014) 'European Union pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer' *Clinical Therapeutics* 36 (2) p. 163-177

[135] Snyder, K. M., Reaman, G., Avant, D., & Pazdur, R. (2013). The impact of the written request process on drug development in childhood cancer. Pediatric blood & cancer, 60(4), p. 531-537.

[136] Vernon, J. A., Shortenhaus, S. H., Mayer, M. H., Allen, A. J., & Golec, J. H. (2012). Measuring the patient health, societal and economic benefits of US pediatric therapeutics legislation. Pediatric Drugs, 14(5) p. 283-294.

5 Direct and indirect benefits

This chapter presents an analysis of the societal benefits of the Regulation and measuring direct and indirect benefits: societal impacts of more effective paediatric treatments as well as other potential impacts related to creating innovative supply chains from research institutes and contract research services to the industry, creating new scientific environment and knowledge, and promoting the rights of children through better access to appropriate health care.

In addition to data collected via the survey to industry, the analysis builds on a two-stage survey (Delphi) to expert stakeholders. The survey questionnaire was sent to experts from across the EU, with 116 people ultimately completing the survey (Phase I Delphi), although some respondents did not answer every question. The background and paediatric sub-speciality of Phase I and Phase II participants are presented in Appendix D. The survey to expert stakeholders was developed based on an exploratory telephone consultations and pilots to uncover issues linked to social and broader economic impacts in the paediatric drug development value chain. The survey collected qualitative and quantitative estimates for the various dimensions of the impact as well as provided a set of open questions to identify further benefits of the Regulation and their impact channels.

The design of the survey questions builds on the evidence gathered via the systematic literature review and the secondary data analysis. This provided an outline of potential benefits/impact drivers of the Paediatric Regulation. The focus of the social impact analysis is to estimate to what extent better treatment (due to more effective medicinal products) reduces the costs of paediatric healthcare treatment due to shorter periods of hospitalisation or fewer adverse drug reactions (ADRs). This may lead to significant reductions in paediatric healthcare expenditure and increased overall savings from reduced child morbidity and mortality. We consider possible monetary and non-monetary impacts. We focus on the following dimensions:

- Availability of and access to medicines result in better treatments and better QoL for children
- Reduction of child-health expenditure, savings from reduced morbidity/ mortality, increased school attendance, and decreased time taken off by parents for caring for their children and adverse drug events

To estimate the monetary value of social savings from improved medical treatment of children as a result of the Paediatric Regulation is very difficult. Vernon et al[137] use US data on discounted life-years, then authors calculate value-added life-years. It is assumed that if off-labelling would have been on-labelling, this would have resulted in a 1% reduction of mortality. The authors then calculate the value of this reduction in mortality using discounted life year valuations. Therefore, using data on hospitalisation and mortality rates in the EU one could refine the model. It should be noted that life year calculations differ

[137] Vernon, J.A. et al., 2012. Measuring the patient health, societal and economic benefits of US pediatric therapeutics legislation - Technical Appendix. *Pediatric Drugs*, 14(5), pp.283–294.

across countries. The EuroVaQ project[138] looking at the European Value of a Quality Adjusted Life Year provides a starting point on computing life year valuations across the EU.

An economic assessment of the second-degree effects of the Regulation, notably, on the research framework created, activities of specialised research centres and CROs, public-private funding created for paediatric medicine, new research knowledge established, and networks formed. A good example is the European Network of Paediatric Research that aims at fostering high-quality paediatric research; helping with the recruitment of patients for paediatric clinical trials; and enabling collaboration between stakeholders.

5.1 Literature review

One of the chief aims of the 2007 EU Paediatric Regulation is protecting the health of children by improving the availability of medicines and dosage information for children. The regulation also intends to stimulate research into paediatric medicines. Thus, the regulation is directly linked to societal impacts such as improved health of children, decreased disease burden and costs to national health systems. Greater availability of published data on the efficacy and safety of medicines will potentially lead to better use of medicines in children.[139] For instance, benefits are expected from new paediatric indications, inclusion of special (class) warnings, specification of dose regimens, timely development of paediatric friendly formulations, and better quality of the clinical evidence.[140]

One of the direct consequences of the new regulatory requirements such as PIPs, even for authorised medicinal products that are currently protected by patents, is the development of formulations and dosages more appropriate for paediatric age groups.[141,142] However, of all the approved PIPs, only 26% and 35% of medicines included trials in young infants and neonates, respectively (Hoppu et al. 2012). Moreover, some authors also argue[143] that PIP decisions can lead to the recruitment of vulnerable children to questionable studies. A similar observation has been made with regard to the PREA in the US. For instance, the necessity of 4 proton pump inhibitor trials for gastrointestinal reflux disease in children has been

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[138] http://research.ncl.ac.uk/eurovaq/EuroVaQ_Final_Publishable_Report_and_Appendices.pdf

[139] Hoppu, K. et al., 2012. The status of paediatric medicines initiatives around the world-what has happened and what has not? *European Journal of Clinical Pharmacology*, 68(1), pp.1–10.

[140] Stoyanova-Beninska, V. V. et al., 2011. The EU paediatric regulation:. Effects on paediatric psychopharmacology in Europe. *European Neuropsychopharmacology*, 21(8), pp.565–570. Available at: http://dx.doi.org/10.1016/j.euroneuro.2010.06.011

[141] Challis, J., 2011. The impact of the Paediatric Regulation on existing medicinal products. *Regulatory Rapporteur*, 8(10), pp.4–7.

[142] Olski, T.M. et al., 2011. Three years of paediatric regulation in the European Union. *European Journal of Clinical Pharmacology*, 67(3), pp.245–252.

[143] Rose, K., 2014. European union pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer. *Clinical Therapeutics*, 36(2), pp.163–177. Available at: http://dx.doi.org/10.1016/j.clinthera.2014.01.009; Rose, K. & Kopp, M.V., 2015. Pediatric investigation plans for specific immunotherapy: Questionable contributions to childhood health. *Pediatric Allergy and Immunology*, 26(8), pp.695–701. Available at: http://doi.wiley.com/10.1111/pai.12500; Rose, K. & Walson, P.D., 2015. The contributions of the European Medicines Agency and its pediatric committee to the fight against childhood leukemia. *Risk Management and Healthcare Policy*, 8, pp.185–205.

questioned as there are differences of opinion among clinicians regarding the condition and its diagnosis.[144]

Between 2007 to 2011, the PDCO made decisions about 682 PIPs; 29 PIPs were completed. Of these, 24 led to new paediatric indications and 77 new formulations. 5 PIPs were completed but did not support the drug's use in children.[145] Similarly, in the US, the BPCA led to 200 labelling changes and 48 instances of new/enhanced paediatric safety information following paediatric clinical trials.[146]

In terms of drugs for rare diseases i.e. orphan drugs, the Regulation did not result in significantly more market authorisations for orphan drugs with a paediatric indication (58% before and 64% after 2007), but did increase the time required to achieve market authorisation.[147]

Another explicit goal of Paediatric Regulation is the reduction in off-label use of drugs. A study from Denmark by Haslund-Krog et al showed that PIPs covered only a small proportion of the drugs that were being used off-label.[148] In Finland, the new legislation has a minor or no impact on off-label use in paediatric inpatients in specialised care: 51% of off-label prescriptions in 2011 vs. 22% in 2001, for new-borns; 21% vs. 5%, for less than two-year-old children; and 24% vs. 3%, for children.[149] These results show that the needs of neonates and children are not yet being fully met by the Regulation. In fact, out of 682 PIPs at the end of 2011, only 110 involved neonates (Turner et al. 2014).

In Europe, the Paediatric Regulation has also led to the creation of a European network of Paediatric Research at the European Medicines Agency (Enpr-EMA). This consists of national and European networks and centres for paediatric research. However, once the initial support for these networks decreased, most networks have not been able to secure sustainable income because enough trials have not been forthcoming or planned trials have been deferred (Hoppu et al. 2012).

A study of the Utah Medicaid Program in the US estimated that a 6-month extension of patent exclusivity cost $2.2m over 18 months following the original expiry date and if extrapolated to the entire US population, the cost was estimated at $430.2m.[150] Moreover,

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[144] Kuehn, B.M., 2012. Laws Boost Pediatric Clinical Trials, But Report Finds Room for Improvement. *Jama*, 307(16), p.1681. Available at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.508.

[145] Turner, M.A. et al., 2014. Paediatric drug development: The impact of evolving regulations. *Advanced Drug Delivery Reviews*, 73, pp.2–13. Available at: http://dx.doi.org/10.1016/j.addr.2014.02.003.

[146] Mathis, L. & Rodriguez, W., 2009. Drug therapy in pediatrics: A developing field. *Dermatologic Therapy*, 22(3), pp.257–261.

[147] Kreeftmeijer-Vegter, A.R. et al., 2014. The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children. *Orphanet journal of rare diseases*, 9(1), p.120.

[148] Haslund-Krog, S. et al., 2014. The impact of legislation on drug substances used off-label in paediatric wards-a nationwide study. *European* journal *of clinical pharmacology*, 70(4), pp.445–52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24398969.

[149] Lindell-Osuagwu, L. et al., 2014. Prescribing for off-label use and unauthorized medicines in three paediatric wards in Finland, the status before and after the European Union Paediatric Regulation. *Journal of Clinical Pharmacy and Therapeutics*, 39(2), pp.144–153

[150] Nelson, R.E. et al., 2011. Patent extension policy for paediatric indications: An evaluation of the impact within three drug classes in a state medicaid programme. *Applied Health Economics and Health Policy*, 9(3), pp.171–181.

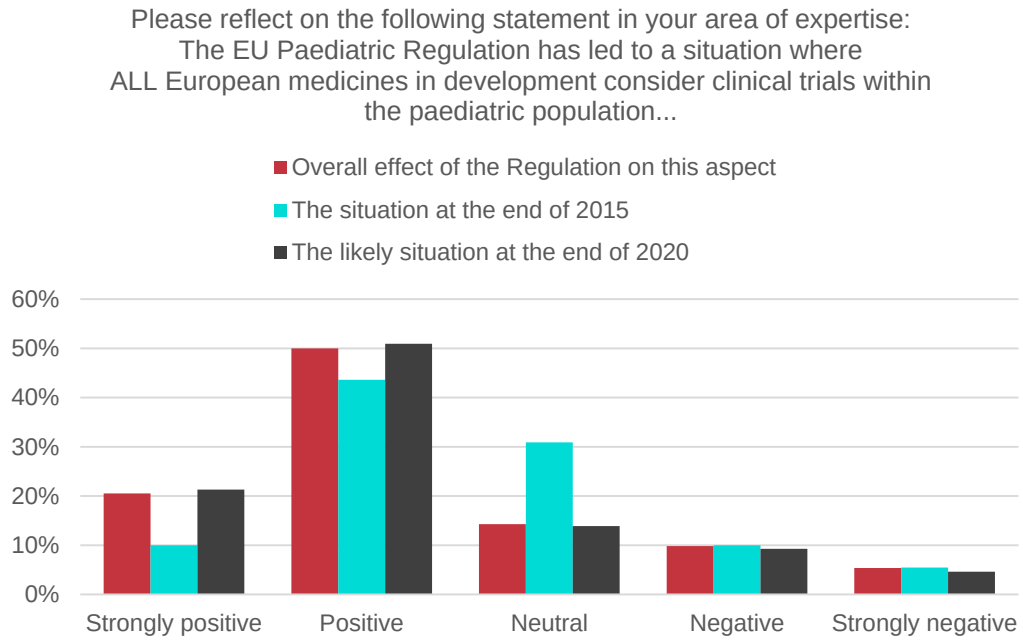
only a minority of these drugs were prescribed to paediatric patients. Furthermore, the BPCA's contribution was estimated to be 3.6m life years gained over the 1997-2009 period; using $100,000 per life-year, this yields $360 billion gross economic benefits according to Vernon et al. 2012 (for more discussion, see Appendix E.1.1).

While there have been more paediatric clinical trials (about 4 times more) over the last decade,[151] which have greatly contributed to knowledge regarding paediatric medicinal products, certain areas of paediatric pharmacology are still under-explored, such as rare conditions and neonates (see, Turner et al. 2014).

5.2 Results of the Delphi Survey

5.2.1 Development of clinical trials within the paediatric population

Figure 25 Delphi survey response to Question 1



Source: Technopolis survey. The number of respondents for each sub-question are: 108, 110 and 112.

For this first question, the survey revealed a broadly positive view overall of the EU Paediatric Regulation's effect on medicines development.

A majority of survey respondents stated that the Paediatric Regulation had led to a situation where all European medicines in development consider clinical trials within the paediatric population. 54% of respondents judged the EU Paediatric Regulation to have had a positive or highly positive effect on companies' behaviour already (2015) in respect to their consideration of clinical trials within paediatric populations for all medicines under

[151] Pansieri, C. et al., 2014. Neonatal drug trials: impact of EU and US paediatric regulations. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 99(5), p.F438. Available at: http://fn.bmj.com/cgi/doi/10.1136/archdischild-2013-305900.

development in Europe. Around 15% of respondents recorded a negative view about this statement, suggesting the regulation has yet to create a situation where all medicines in development will consider paediatric clinical trials.

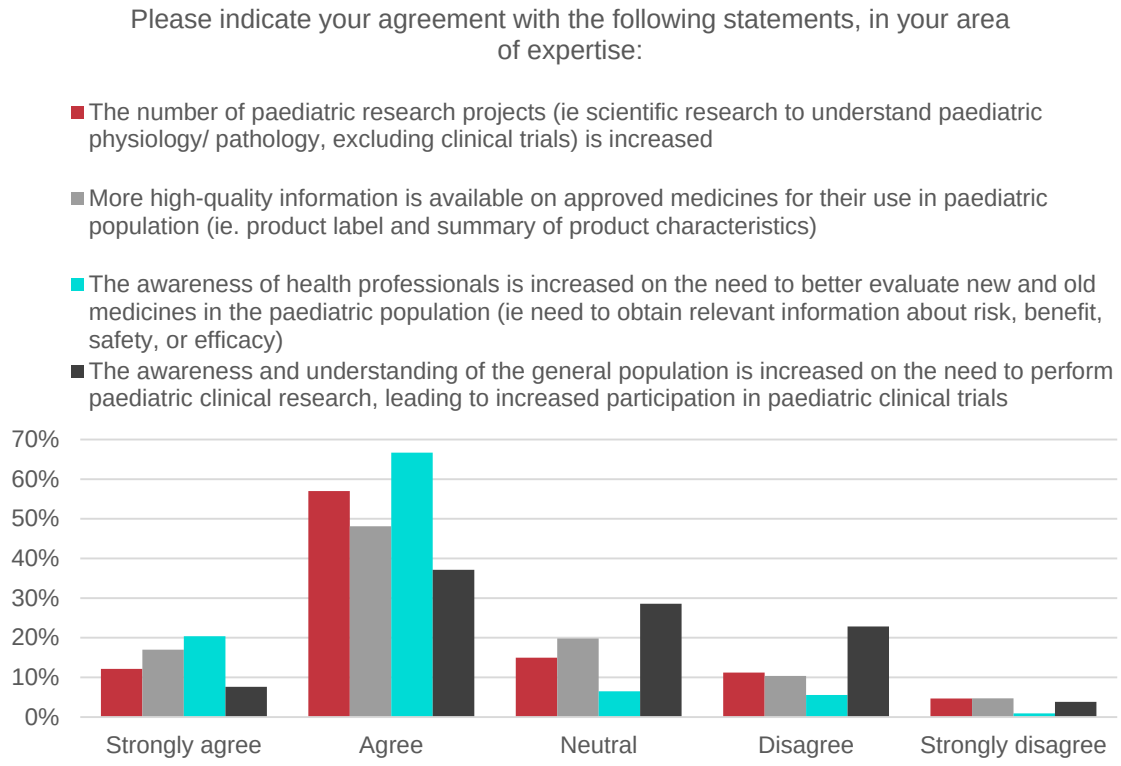
The survey found that a larger majority expect the regulation will have had an important and positive effect on European medicines development by 2020. Over 70% of respondents signalled a positive view of the likely situation at the end of 2020. Positive developments referred to include the initiation of early consultation of clinicians by sponsors to better consider patients' needs and improvements in the data on dosing, safety, and efficacy in children.

The swing in positive votes between 2015 and 2020 is largely driven by the switching of votes from neutrals to positives. The proportion of sceptics was largely unchanged: around 14% of survey respondents view the likely situation at the end of 2020 negatively as compared with around 15% for 2015. Respondents provided additional comments in which they expressed reservations about progress and notable concerns included the following:

- Relatively small number of marketing authorisations of paediatric medicines, to date
- Slow progress in certain therapeutic areas e.g. oncology, psychiatry as well as in neonatology
- Concerns over the PIP waivers granted
- Scarce (EU) funding provision to sustain future paediatric medicine developments
- Continued use of off-label medicines for children
- Concerns over long delays in the process and deferrals

5.2.2 *Increase in research, awareness and information*

Figure 26 Delphi survey response to Question 2



Source: Technopolis survey. The number of respondents for each sub-question are: 107, 108, 105, and 106.

Survey respondents were asked to what extent they agree with four statements (see Figure 26).

69% of the respondents agree or strongly agree that the number of paediatric research projects is increased. 16% of the respondents disagree or strongly disagree with this statement, one of whom went on to write that there has not been *enough* progress, and to list several studies in support of that position. One of the references included a study by Van Riet et al. (2016)[152] that analysed the availability of licenced paediatric drugs and the development of new indications or new routes of administration for the paediatric population. This study concludes that "further research in some areas of paediatric drug development is required in order to ensure that paediatric drugs are age-appropriate and of the required standards, e.g. safety of excipients, acceptability testing".

65% of the respondents agree or strongly agree with the statement that more quality information is available on approved medicines for their use in paediatric population (i.e. product label and summary of product characteristics). 15% of the survey respondents disagree with this statement.

[152] Van Riet et al (2016). Paediatric Drug Development and Formulation Design a European Perspective. AAPS PharmSciTech

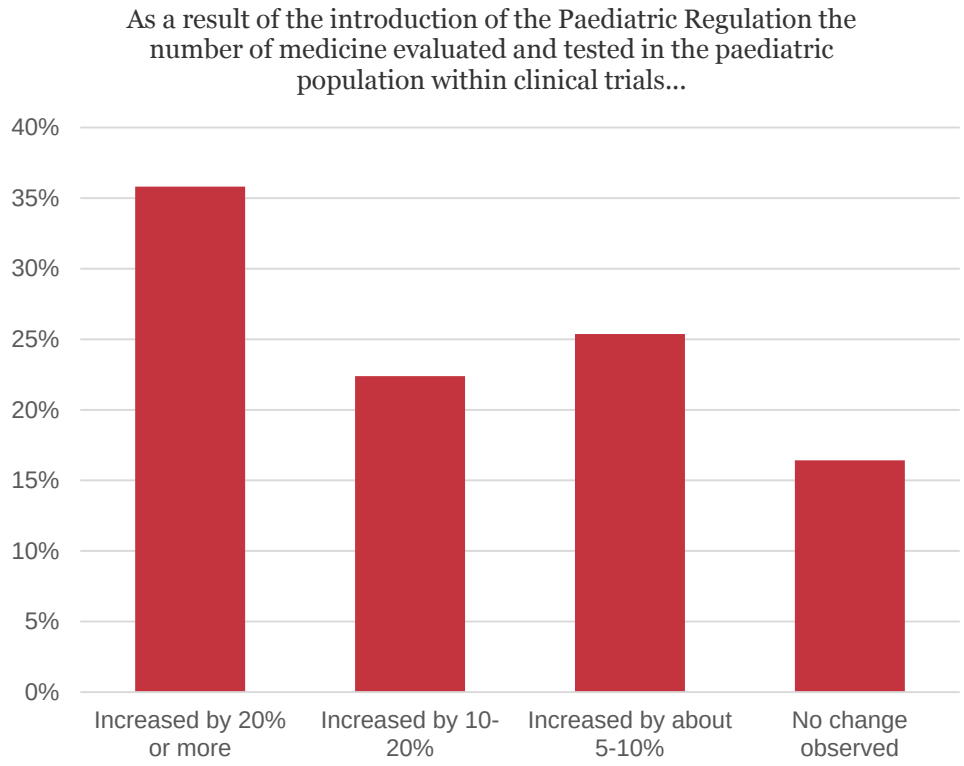
87% agree that the awareness of health professionals has increased as regards the need to better evaluate medicines in the paediatric population. A small minority, 7% of the respondents, disagrees with this statement. A wider range of international paediatric networks (e.g. TEDDY, PENTA, PRINTO) and research consortia have been established in Europe, some with the support from the European Commission (EC) and following the introduction of the Paediatric Regulation. GRiP (Global Research in Paediatrics) and SMART (Small Medicines Advanced Research and Training) are developing training programmes to increase the quality and the methodological level of paediatric clinical research. As a result, public-private partnerships have been able to mobilise the scientific and clinical community to devise clinical development plans that are acceptable to regulators and conduct clinical studies.

There is no consensus as to whether the awareness of the general population has increased as regards the need to perform more paediatric clinical research or the related need for increased participation in paediatric clinical trials. 47% of respondents judged that the awareness of the general population has increased, following the introduction of the regulation. For example, one respondent noted that the regulation had made it easier to explain the importance of allowing children to participate in clinical trials. A significant minority (27%) of respondents disagreed. Several respondents went on to write that awareness of these issues outside of the pharmaceutical industry remains poor. One contributor wrote that more time is needed to see any substantive effect of the regulation on the increased awareness among the general population, simply as a result of the long development phase, deferrals, modifications to PIPs etc., (only a small proportion of paediatric products have labelling changes as a result of the regulation). Several other respondents argued that the impact on awareness would have been greater if more (EC) support had been devoted to communications campaigns. Respondents referenced several papers that explain the importance of communication, including an earlier study by the RCPCH (2012) highlighting the practical challenge faced by those wishing to increase volumes of paediatric research due to the general difficulties of engaging patients and other members of the public in trials in part because of a limited appreciation of the importance of such work.[153]

[153] RCPCH (2012) Turning the Tide http://www.rcpch.ac.uk/system/files/protected/page/Turning%20the%20Tide%20Full%20Report.pdf Research Capacity Survey: http://www.rcpch.ac.uk/system/files/protected/page/Research survey report FINAL (wingsan).pdf Infants, Children's and Young People's Child Health Research Charter: http://www.rcpch.ac.uk/improving-child-health/research-and-surveillance/infants-children-and-young-people's-research-charte

5.2.3 *Changes in the evaluation, testing and approval of paediatric medicine*

Figure 27 Delphi survey response to Question 3a



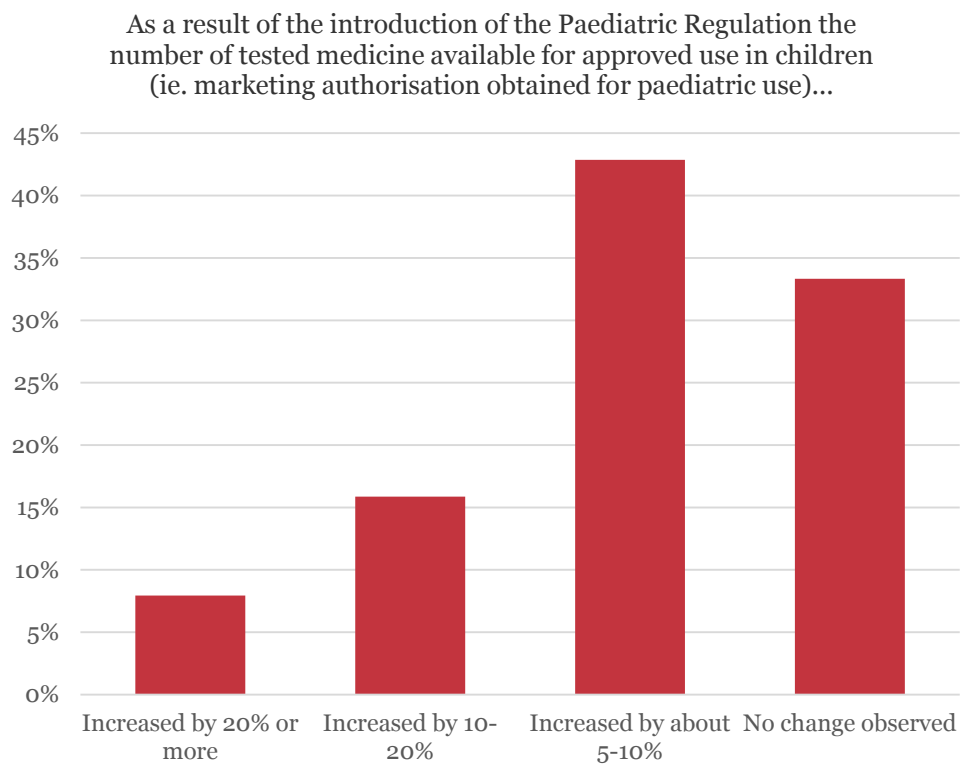
Source: Technopolis survey. The number of respondents is 67.

Question 3 invited respondents to estimate the effect of the regulation on the number of medicines being tested through clinical trials in the paediatric population, and to indicate extent of any such change, see Figure 27.

The overall results are encouraging, with 84% of respondents indicating that there had been a measurable increase in the numbers of medicines tested within paediatric populations in the period since the implementation of the regulation, with more than a third suggesting the regulation had led to an increase of 20% or more. Respondents felt that without the regulation, the paediatric studies, agreed as part of a PIP, would not have taken place.

16% of respondents reported no observable change. One respondent noted that a number of waivers had been granted. Another respondent argued that while the European Clinical Trials Database (EudraCT) shows there has been an increase in paediatric clinical trials, it may not in whole be the result of the Paediatric Regulation as the increase mirrors a wider trend of increasing numbers of adult and mixed clinical trials.

Figure 28 Delphi survey response to Question 3b



Source: Technopolis survey. The number of respondents is 63.

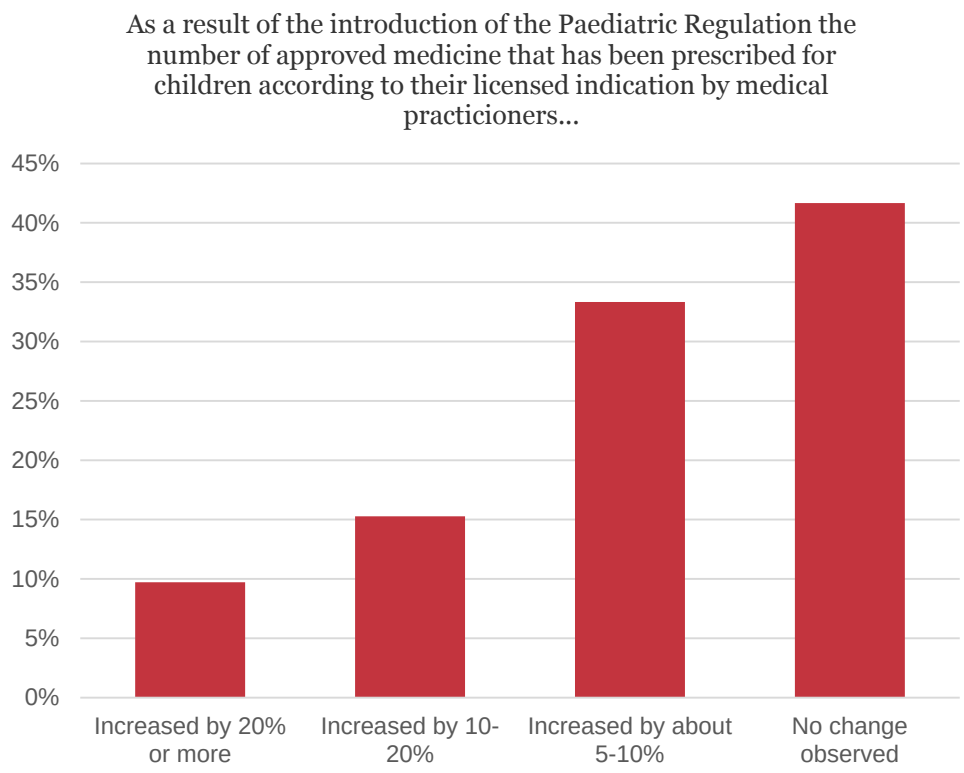
The survey asked people to indicate if, as a result of the introduction of the Paediatric Regulation, the number of tested medicines available for approved use in children had increased (Figure 28). The majority of survey respondents indicated that there was an increase (67%) and 43% of respondents estimated that the increase was in the range 5-10%. In addition, respondents flagged the fact that many PIPs are still ongoing, and some have been deferred, and that more medicines would be approved in the near future. For example, in oncology or psychopharmacology, a substantial proportion of the drugs that are used to treat children are still used off-label and, in particular in this therapeutic area, there may not be sufficient research/support for research[154] A study by David C. Radley et al. (2006) found that 73% of off-label use had little or no scientific support.[155] A 2009 study by Alicia Bazzano et al. found that 62% of U.S. paediatric visits from 2001-2004 included off-label prescribing, with younger children at higher risk of receiving off-label prescriptions.[156]

[154] See also the study of Persico et al. (2015). Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives. Eur Neuropsychopharmacol, 25(10): 1513-31.

[155] David C. Radley; Stan N. Finkelstein; Randall S. Stafford (2006). Off-label Prescribing Among Office-Based Physicians. Archives of Internal Medicine 166 (9): 1021–1026.

[156] Alicia Bazzano MD MPH; Rita Mangione-Smith MD; Matthias Schonlau PhD; Marika Suttorp MS; Robert Brook MD ScD (2009). Off-label prescribing to children in the United States outpatient setting. Ambulatory Pediatrics 9

Figure 29 Delphi survey response to Question 3c



Source: Technopolis survey. The number of respondents is 72.

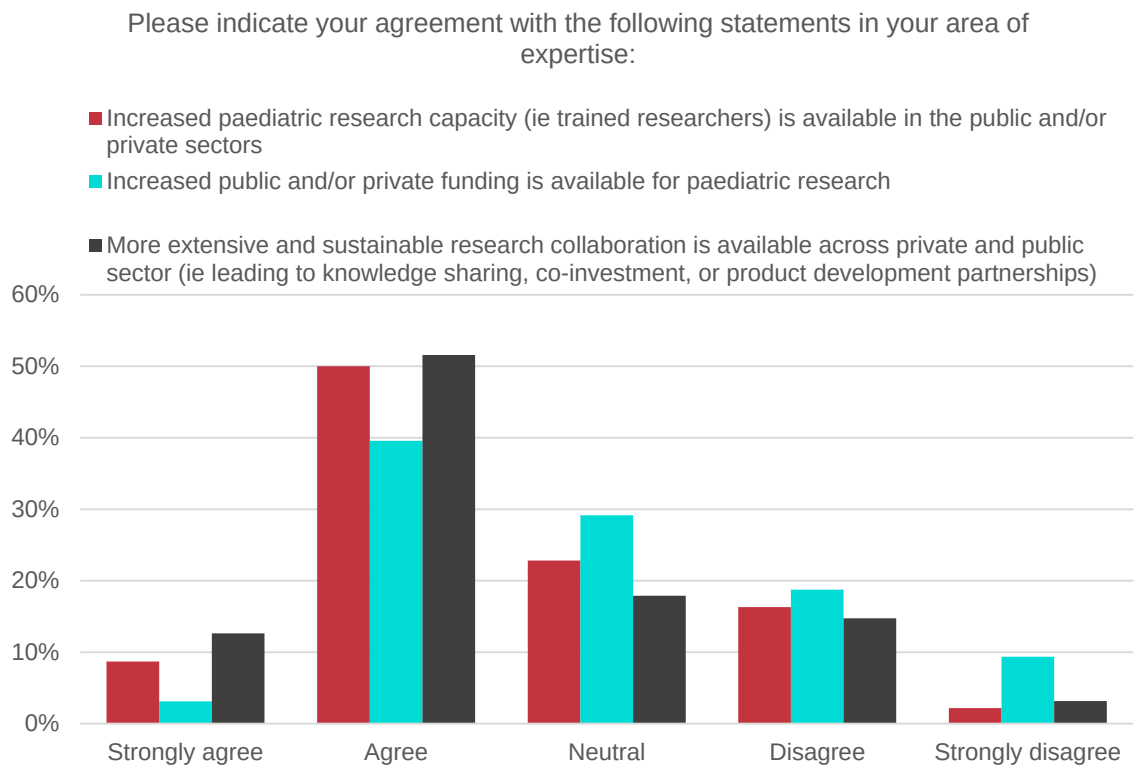
On the question of prescription, a small majority of respondents, 58%, indicated that medical practitioners are increasingly prescribing approved medicines according to their licensed indication for children, as a result of the Paediatric Regulation.

The majority of respondents that reported an increase in prescriptions, estimated the scale of that increase was in the range of 5-10%. Several contributors went on to provide written comments noting the large volume of PIPs that are yet to achieve marketing authorisation and the natural time lag that this creates, with only limited numbers of new or newly indicated medicines available to be prescribed.

Survey respondents also noted that paediatric drug development had been swifter in some therapeutic areas, e.g. antibiotics, and less swift in others, e.g. oncology and tuberculosis. Respondents also noted that paediatric drug development for infants and neonates is particularly slow (lagging); and that many medicines have not yet been tested and are currently often used off-label.

5.2.4 *Change in research capacity, funding and collaboration*

Figure 30 Delphi survey response to Question 4



Source: Technopolis survey. The number of respondents for each sub-question are: 92, 96 and 95.

In question 4, respondents were asked to indicate the extent to which they agreed with each of three statements about paediatric research (see Figure 30): Increased paediatric *research capacity* is available in the public and/or private sectors; Increased public and/or private *research funding* is available for paediatric research; and More extensive and sustainable *research collaboration* is available across private and public sector (i.e. leading to knowledge sharing, co-investment, or product development partnerships).

The survey revealed a broadly positive view about improving research capacity (60% in agreement) and research collaboration (65%), with a somewhat more neutral view expressed about any improving trend in paediatric research funding in the period since the introduction of the regulation. A substantial proportion of the respondents are neutral (neither agree not disagree) and a slightly smaller proportion disagree/strongly disagree (18%, 28% and 18%) with these statements.

Survey respondents provided several arguments that explain the lack of consensus around the statements:

- Capacity building: several respondents argued that developments had been very positive and that, as a result of the regulation, institutions had been able to build bigger teams working with clinical trials in children. However, other respondents wrote that the

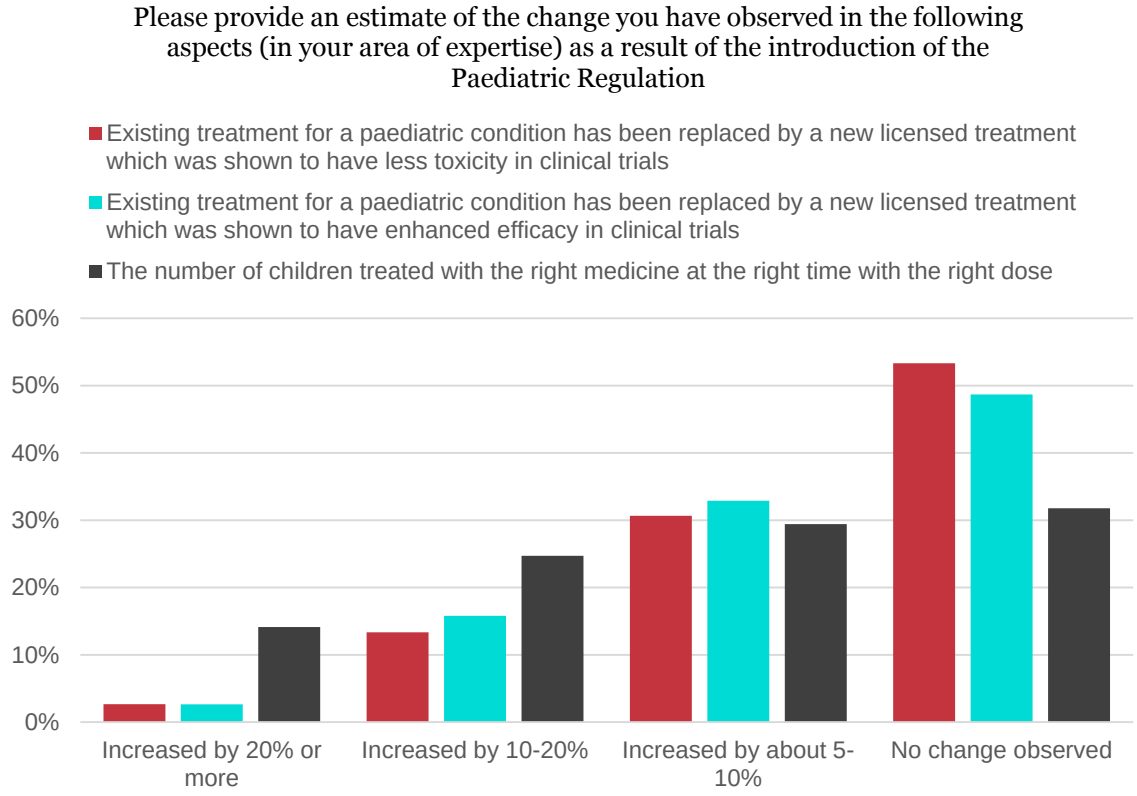
expansion in research capacity had been patchy and looked very different across therapeutic areas and institutions. It was argued that (in some cases) capacity building was considered only after the regulation came into force and that as no specific funding was available for infrastructure development, one inevitably saw rather uneven progress.

- Research funding: one contributor argued that when the paediatric legislation came into force, there was an increase in funding and paediatric research collaboration but that this increase in funding had been interrupted and industry continues to focus on adult drug development and less on paediatric drug development, where financial returns are less interesting.[157] Other contributors noted that there is substantial variation in the support for paediatric drug development across national governments. Several others remarked on the shortcomings of the Commission's main research instruments, FP7 and Horizon 2020, stating that the funding instruments were poorly adapted to the needs of clinical trials in children.
- Collaboration: In some therapeutic areas the regulation is thought to have increased multi-stakeholder dialogue and cooperation, e.g. on childhood cancer drug development but in other therapeutic areas collaboration was reported to be poor still with no new networks for collaboration having been established. Also, it was suggested that the regulation had led to more industry-led research, while having had little or no effect on the volume of collaborative research (public private) or investigator-led research (public, academic).

The RCPCH (2012) Turning the Tide report find that only 5% of research funding is spent on child health research

5.2.5 *Changes in the treatment of the paediatric population*

Figure 31 Delphi survey response to Question 5



Source: Technopolis survey. The number of respondents for each sub-question are: 75, 76 and 85.

Survey respondents were asked to reflect on whether the introduction of the Paediatric Regulation had led to an improvement in the treatment of the paediatric population on one or more of three dimensions: i.e. less toxic medicines; more efficacious medicines; increases in the numbers of children and young people treated with the right medicines at the right time and with the right dosages, see Figure 31. Regarding the replacing of existing treatments for a paediatric condition (either by treatment with less toxicity or enhanced efficacy), close to half of the respondents stated that the regulation had led to an increase (47%, 51%). While 68% stated that there had been an increase in the number of children treated with the right medicine at the right time with the right dose. In all three cases, most respondents opted for an increase of around 5%-10% in the numbers of 'correct' treatments.

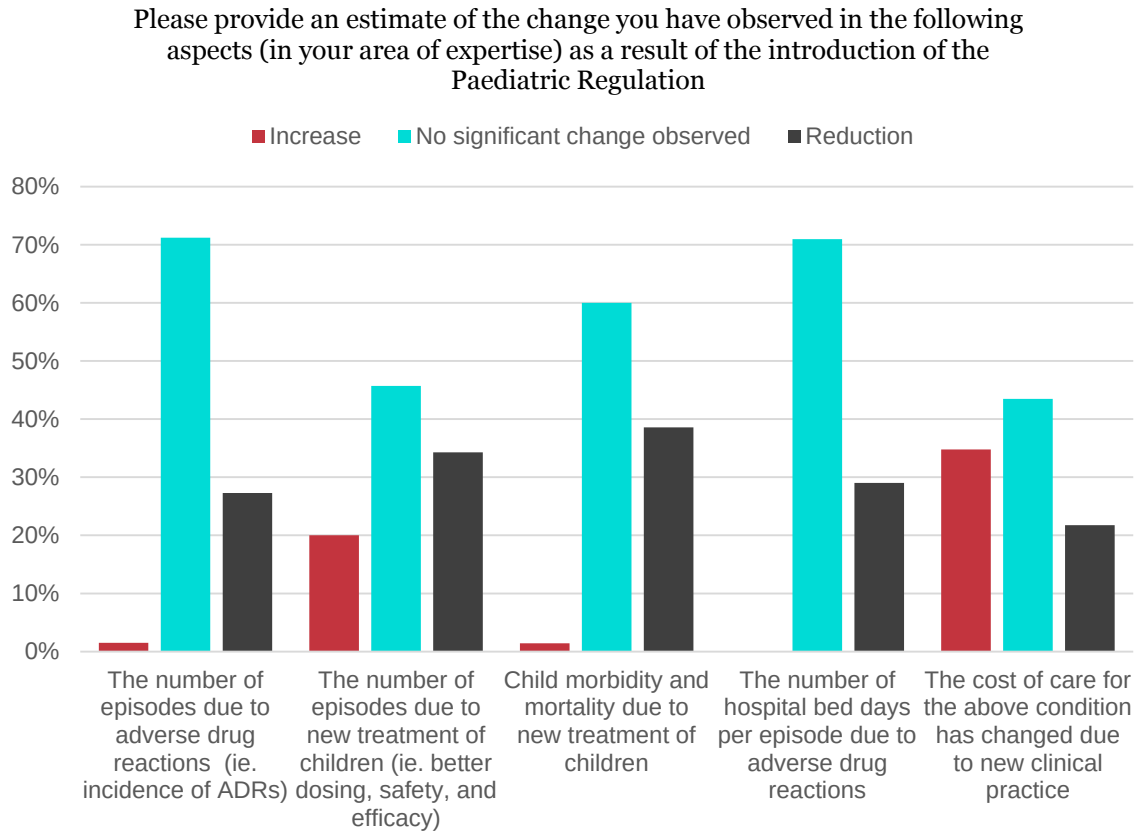
Several respondents wrote stating they had difficulty in attributing changes in treatment to the Paediatric Regulation alone, while others acknowledged that there had been some limited progress, involving quite small steps so far as regards to efficacy and toxicity in general but more progress around specific treatments such as anti-rheumatic, immunosuppressive drugs and anti HIV drugs.

Others noted that the regulation has begun to make a difference, however, the rather complex and involved development process inevitably slows the rate of progress and arguably reduces the absolute potential for change:

- The need for certain drugs and for age-appropriateness of drug forms and formulations still exist. To date, only a small percentage (24 out of 135, about 18% of the total for 2007-2013 according to one survey respondent) of active substances included in the Priority Lists of off-patent drugs issued are subject of an agreed paediatric development in a PIP"[158].
- A very low number of PUMAs are granted, i.e. only 2.
- Paediatric off-label use has not been reduced.[159]

5.2.6 *Health and wellbeing of children and cost of care*

Figure 32 Delphi survey response to Question 6



Source: Technopolis survey. The number of respondents for each sub-question are: 66, 70, 70, 62, and 69.

[158] E.g. see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/05/WC500206082.pdf for an updated list of existing therapeutic needs in the paediatric population. See also van Riet-Nales, DA, et al, 2011

[159] Lindell-Osuagwu et al 2014, Piñeiro Pérez et al 2014

Question 6 invited respondents to judge the effect of the regulation on several wider issues, from child morbidity to the costs of care. These wider effects are difficult to identify and measure in any definitive sense, and so we invited people simply to provide an indication of the direction of any changes they had observed in their own area of expertise and which they would feel confident in attributing to the introduction of the regulation.

Survey respondents were asked to indicate any observed change (as a result of the Paediatric Regulation) on: adverse drug reactions (ADRs), the number of episodes, child morbidity, the number of hospital bed days due to ADRs, and on the cost of care. As expected, people found the five questions difficult to answer, however, around 60% of all respondents did provide answers.

For each impact type, 40-70% of respondents indicated that they had observed no significant change. While most people had not yet observed any meaningful changes, there was a significant minority of respondents that judged the regulation to have had a positive impact on these different dimensions (i.e. reduction in the value of these indicators).

Almost 40% of respondents indicated they had seen improvements in child morbidity in their field, which they would attribute to the regulation. Around 30% of respondents had observed improvements in other impact types, from the incidence of ADRs to the number of related hospital bed days.

20% of the survey respondents find that the number of episodes due to new treatment of children has increased[160] and 35% of the survey respondents indicated that the cost of care had increased due to new clinical practices / prescriptions. New products developed for paediatric use can be relatively more expensive, e.g. there can be cost increases related to the licencing of new medicines.

In addition to inviting respondents to indicate the broad direction of travel, the survey asked people to estimate the degree of change they had observed, see Table 24. On child morbidity, 29% of the respondents judged morbidity had improved by 5-10%, 4% argued that it had improved by 10-20% and 6% argued it had decreased by 20% or more. The cost of care was the one dimension where a large minority (35%) indicated there had been a negative impact, with the new treatments and treatment regimens leading to an increase in costs, possibly leading to issues of accessibility.

[160] Note that the authors of this paper have no clear understanding why this should be the case and whether respondents may have misunderstood the question: The chart suggests that around 33% of respondents have seen a reduction in the number of episodes as a result of the use of more efficacious paediatric drugs or more appropriate dosing regimens. The chart also suggests that 20% of respondents have seen an *increase* in the numbers of episodes, as a result of better drugs / dosing. This last point seems counter-intuitive.

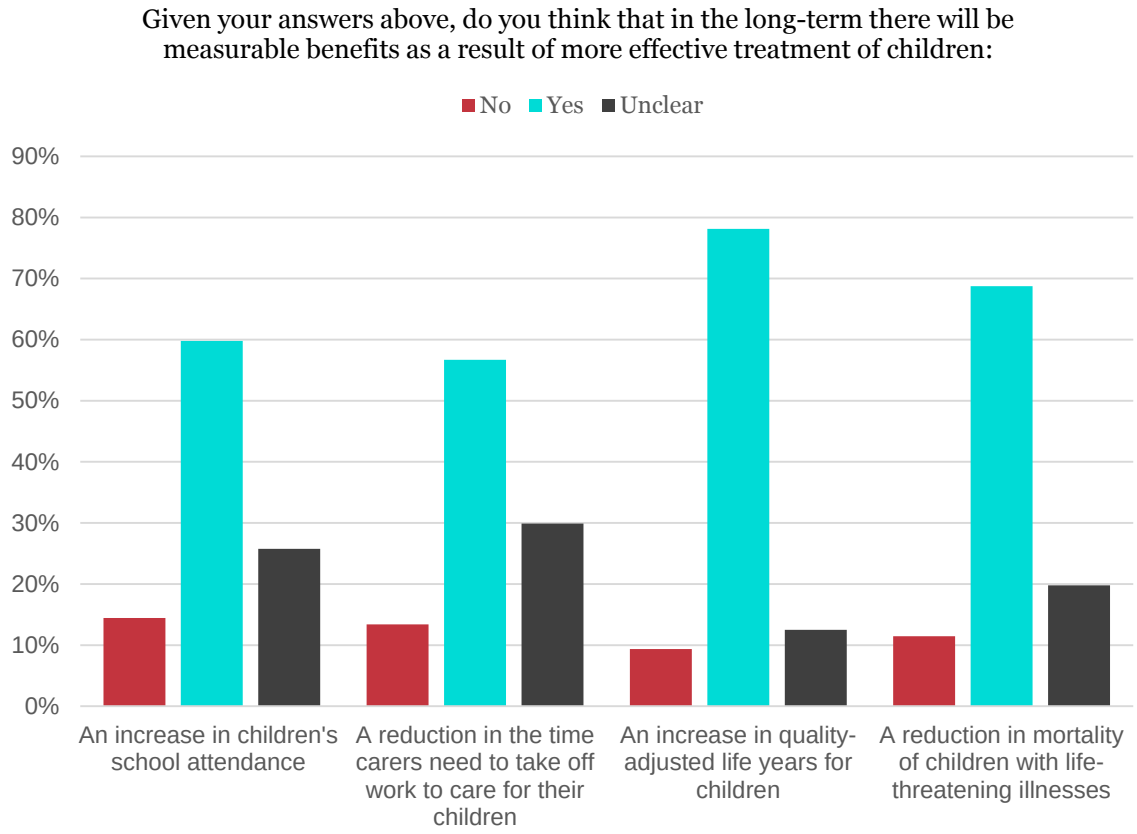
Table 24 Survey response to Question 6, full results on health and wellbeing of children and cost of care

	The number of episodes due to adverse drug reactions (i.e. incidence of ADRs)	**The number of episodes due to new treatment of children (i.e. better dosing, safety, and efficacy)**	**Child morbidity and mortality due to new treatment of children**	**The number of hospital bed days per episode due to adverse drug reactions**	**The cost of care for the above condition has changed due to new clinical practice**
Increased by 20% or more	0%	4%	0%	0%	16%
Increased by 10-20%	0%	0%	1%	0%	10%
Increased by about 5-10%	2%	16%	0%	0%	9%
No significant change	71%	46%	60%	71%	43%
Reduced by 5-10%	20%	26%	29%	16%	12%
Reduced by 10-20%	5%	9%	4%	13%	9%
Reduced by 20% or more	3%	0%	6%	0%	1%

Source: Technopolis survey. The number of respondents for each sub-question are: 66, 70, 70, 62, and 69.

5.2.7 *Long-term benefits*

Figure 33 Delphi survey response to Question 7



Source: Technopolis survey. The number of respondents for each sub-question are: 97, 97, 96 and 96.

Question 7 invited respondents to go one step further in considering wider socio-economic impacts. In addition to estimating the impact of the Paediatric Regulation on Health and wellbeing of children and the cost of care, respondents were asked to indicate if, in the long-term, the regulation would have a measurable benefit on:

- Children's school attendance
- Time cares need to take off work to care for children
- Quality-adjusted life years for children
- Mortality rates of children with life-threatening illnesses

As presented in Figure 33, the majority of respondents, i.e. 60%, 57%, 78%, and 69% respectively, expect there will be measureable benefits. The remainder of respondents are either unclear about the impact or judge there will be no measurable benefits (9%-14%). Some of the respondents that answered negatively are of the opinion that there are no better treatments on the market at this point in time, and for this reason there can be no measurable improvements in these wider areas. Another respondent questioned the degree to which long-term benefits attributable to the Regulation will be measurable, while arguing that there will be desirable benefits of many kinds, in terms of more age-appropriate

formulations, the facilitation of easier, more precise dosing, and the availability of paediatric dosing information.

Amongst those that were positive with regards to measuring longer-term benefits, several noted that there have been benefits already in disease areas that will eventually have a positive impact e.g. mortality. It was also noted that developments in the treatment of neonates will take another 10-20 years to flow through to measurable impacts, and that such developments are dependent on, amongst other, continued funding.

Various other benefits were mentioned, and these are listed below:

- Benefits to patients and consumer groups
  - Greater awareness on paediatric needs and the importance of testing drugs in the paediatric population
  - Greater awareness in the level of health literacy of the general population
  - Involvement of the paediatric population in early discussions on drug development
  - Increase in evidence based prescriptions / dosing information
  - Availability of more age-appropriate formulations
  - Social benefit in pursuing better medicine for children and access to licensed medication
  - Opportunity for greater awareness about the costs of medical care
  - Early access to new treatments and medications via clinical trials which may also e.g. lead to shortened disease profiles, shorter hospital / treatment periods, better health, and a decrease of health care costs
- Benefits to industry
  - Change of culture, more inclusive focus on developing new and improved medicine for the paediatric population
  - Increase in competiveness within the European market producing benefits to taxpayers and patients, e.g. the EU market is becoming more attractive for FDI because the Paediatric Regulation offers a stable regulatory framework; opportunities for commercial clinical trial investment and attracts research from outside the EU
- Increase in jobs and growth as a result of the increased investment in R&D

5.3 Results from the survey to industry

The survey to industry asked to indicate the wider benefits of the Paediatric Regulation. In response, one survey participants noted that, “despite modest achievements so far in terms of rewards, the societal benefits from the Paediatric Regulation cannot be underestimated”.

- Several survey respondents remarked that the regulation has provided access to new and improved medicine. Some respondents referred to an improvement of the quality of care provided to the patients and others referred to better health in children. Moreover, respondents referred to the development of more age appropriate formulation as well as a reduction in off-label use.

- Several survey respondents find that the regulation generated new training, research capacities and knowledge to industry, eg about PK/correct dosing, safety and efficacy of medicines in children.
- Several survey respondents find that the regulation generated new knowledge for prescribers, and has led eg to basing paediatric dosing more on scientific studies, better information on the importance of well tested / approved medications for children and the importance of correct dosing. Other comments included the increase in documentation of error rates in diluting for off label use and the increase in more updated product information. One respondent finds that the regulation led to the development of dissemination/communication strategies that have addressed laymen and the healthcare professionals' community as well.
- Several respondents commented in the fact that the regulation has improved networks:
  - Increase in the involvement of researchers from academia or public research institutions in paediatric drug development programmes
  - Integration of patients and families into the design and conduct of research and trials increasing their awareness and competence
  - Setup of public-private collaborations sharing of ideas, business, opportunities and innovation
  - Development of collaborations with clinicians enquiring other pharmaceutical and clinical developments
  - Creation of new research networks
- Some survey respondents remarked that the Paediatric Regulation evoked a change in culture. One respondent reported a significant shift in mind-set within pharmaceutical companies and noted that the regulation helped encourage paediatric development become a more integral part of the overall development of medicines in Europe.

  Another respondent remarked that the regulation put the paediatric issues at the core of the European agenda and another remarked that it has become an integral part of the overall development of medicines in Europe.

6 Cost-benefit assessment model

This chapter describes the development of a cost benefit assessment model of the Regulation based on a systematic overview of all relevant impacts (both direct and indirect) of the measure. The model is populated as far as possible with realistic data to arrive at an exploratory analysis of the costs and benefits of the Regulation in the period between 2007-2015.

Policy background and objectives

The Paediatric Regulation is based on the assumption that Paediatric Investigation Plans (PIPs) will lead to a better understanding of the positive and negative impacts the use of a given medicinal product may have on treating children with it. A core effect expected is that a switch from off-label to on-label use will improve treatment by a better focused application of the medicine to cases where its effect is most probable, and that adverse drug reactions will be reduced. Pharmaceutical companies have argued that the extra cost resulting for health systems from extending the supplementary protection certificate (SPC) by 6 months, and thereby granting the marketing authorisation holder a 6-month bonus on its monopoly rent, is more than justified by the additional benefits resulting from this for society, particularly due to the many deaths of children avoided.[161]

Figure 34 illustrates the relation between the launch of new and improved medicine for children and the positive effect on society from improved medicine. This relation is explored in section 6.2, where the estimated benefits are presented, which may be derived from adverse drug reactions (ADRs) avoided due to the improved information on how to apply better medicinal products under analysis to children. These benefits are to be contrasted with the cost to society resulting from the extra monopoly rent obtained by pharmaceutical industry, wholesalers, pharmacies and in some countries by governments from extra value added/sales tax levied.

The WHO defines an ADR as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man.” Obviously, in a concrete instance, it is very difficult to indeed prove that it was a particular drug, and not any other of the many potentially intervening variables, that caused the harm to the patient. And quite often they are confounded with adverse drug events (ADEs), defined as “any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury.” Subsets of ADEs are some types of medication errors (MEs), ADRs, and other “undesirable experience associated with the use of a medical product in a patient.” Note that “associated” does not imply a causal relationship as for ADRs. In the end, only data available from FDA and EMA remained as a base to estimate the type and prevalence of ADEs. These data do not single out ADRs, i.e. the percentage of adverse events having a causal relationship to the drug under investigation remains unknown, but is in any case lower.

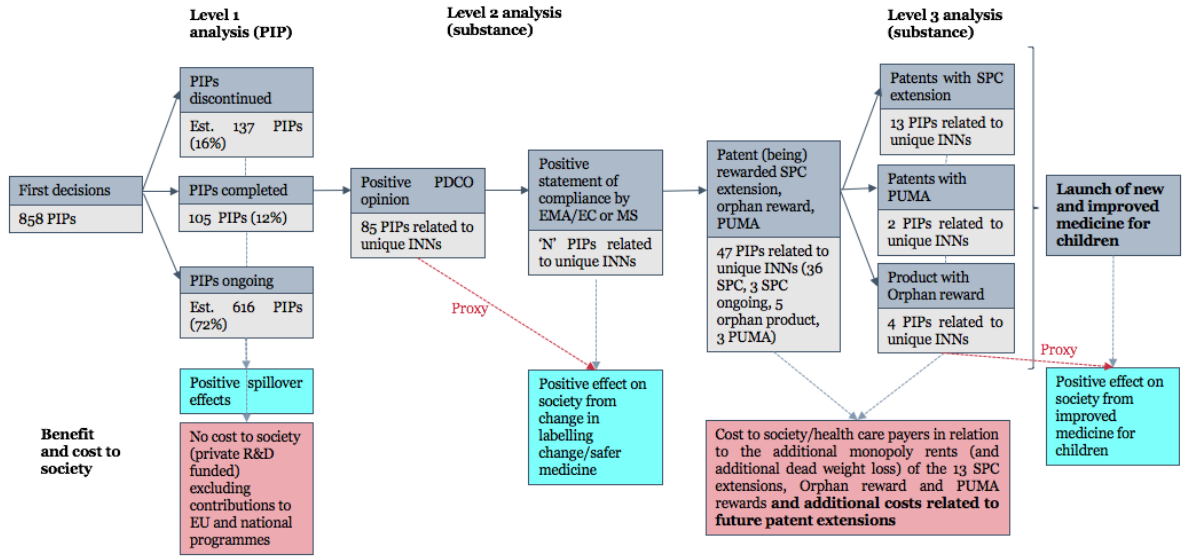
The incidence of an ADE relates to a specific child undergoing a therapeutic intervention with the medicine in question. For this study, it is termed a treatment episode – a core concept for

[161] Vernon, J. A., Shortenhaus, S. H., Mayer, M. H., Allen, A. J., & Golec, J. H. (2012). Measuring the patient health, societal and economic benefits of US pediatric therapeutics legislation. Pediatric Drugs, 14(5), 283-294.

the benefit-cost analysis. Consequently, in order to approach the issue of ADEs, a first step in our overall calculations to populate the Cost-Benefit Model was to arrive at a rough estimate of the number of paediatric treatments resulting from the use of the medicinal product under investigation during the 6-month extra SPC period. In line with this, all of the data reported cover this 6-month period unless otherwise stated. It should be noted that no valid, reliable - and therefore comparable - and representative data on ADRs are available. The CBA model builds on limited data and assumptions.[162]

Figure 34 also explains that those PIPs that have already received a positive statement of compliance, but not (yet) granted SPC extension, are expected to have a positive effect on society resulting from the change in labelling/safer medicine (level 2 analysis). These benefits are presented in section 6.3. Finally, it is thought that the R&D investment the pharmaceutical industry undertakes in compliance with the Paediatric regulation has positive spillover effects (level 1 analysis – highest level analysis). Section 6.4 elaborates on this hypothesis.

Figure 34 Overview of the relation between costs and benefits of medicine for children and the Paediatric Regulation



6.1 The cost-benefit analysis approach

A generic socio-economic cost benefit analysis (CBA) is a systematic overview, analysis and summary of all impacts (both financial and non-financial) of a (policy) measure, which are deemed relevant for decision making. The aim of a CBA is to determine whether a measure is desirable, i.e. whether from the point of view of the respective decision making person or body the expected benefits exceed those of the expected costs involved – be it at the level of a private organisation, a public body, or society. In cases where alternative paths of action are available, it will also help to identify the most advantageous alternative.

[162] The context of such studies usually relates only to a certain setting like a single or a group of hospitals at the secondary or tertiary level, the ambulatory setting of emergency rooms, community centres etc. in a certain town or region, often also concerning only a given disease.

In the healthcare system, this can be done from different perspectives, taking into account those costs and benefits that impact on a particular entity: the private perspective of a given stakeholder, the patient's perspective, the healthcare system perspective or the social welfare perspective, in which also external costs and benefits are taken into account and transfers (e.g. taxes) are left out. In all perspectives the CBA method calculates the net present value (NPV) of current and future socio-economic cost and benefits of a specific intervention, a project, or a policy and its implementation strategy and measures.

The CBA can be applied - in principle - to any context and policy decision situation, be it in the public arena or a commercial context. It will depend on the decision-maker's perspective which benefits and costs, measured in which fashion, and based on which assumptions, expectations, extrapolations should enter into the overall "equation". It is this feature which allows to test assumptions or expectations and their likely impact, and to choose from alternative application scenarios and options which have the highest likelihood to achieve a particular policy objective.

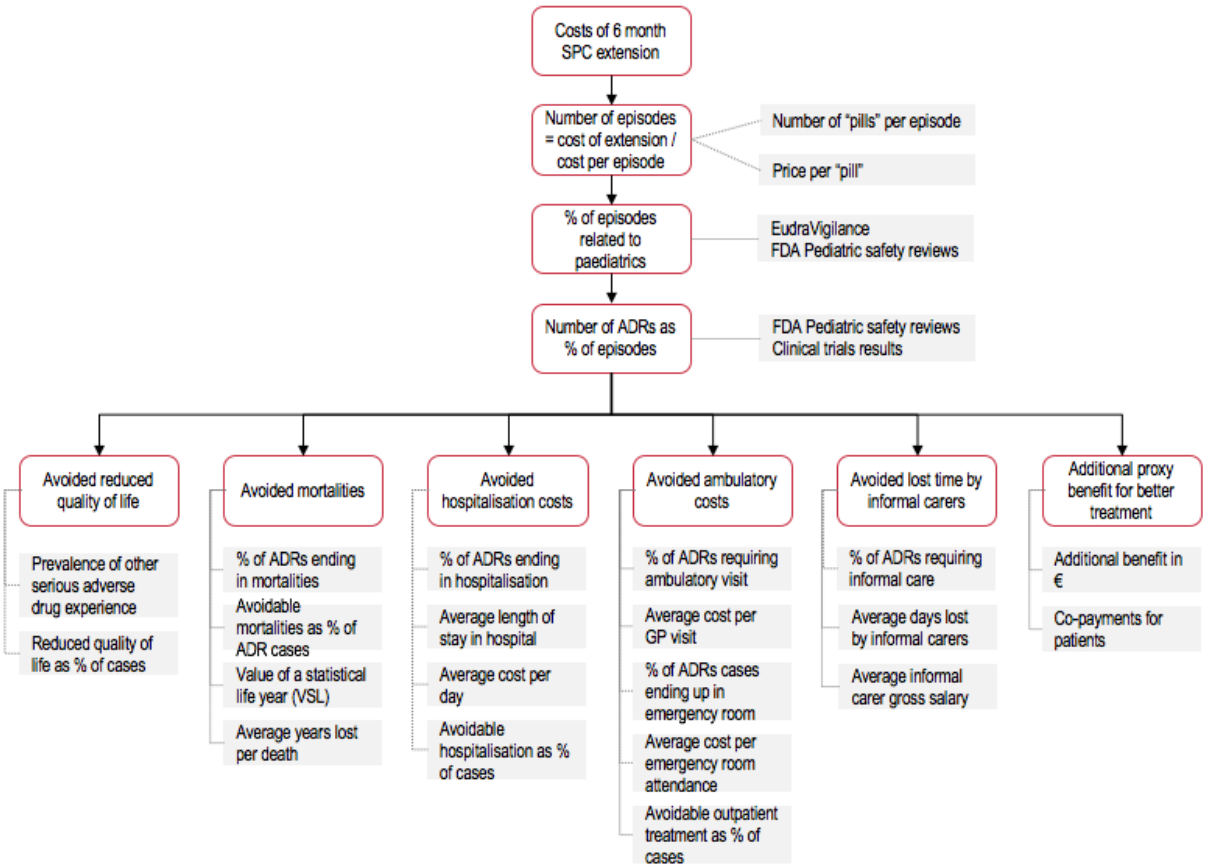
There are very little literature or grey reports available discussing the issue of the potential socio-economic return on the extra monopoly rent reaped by pharmaceutical companies holding a market authorisation for a medicine which was awarded an extra 6-month SPC after successful execution of a PIP. These extra costs accrue to the healthcare system and to each individual patient concerned – either directly or via contribution to healthcare related taxes and health insurance payments. It is assumed that children which take the medicine in question, and indirectly others, will considerably benefit from better treatment outcomes. These benefits may relate to:

- Improved paediatric care through added precision in the use of pharmacotherapy in paediatric populations
- Reduced ADRs and burden of paediatric diseases
- Shorter periods of hospitalisation

In return, these benefits may contribute to lower consumption of medicinal products through better targeting of treatment. However, it is also possible that these benefits will lead to an increase in the consumption of medicinal products as a result of the potential improved access to medicines. This means that more children could be treated with the right medicine. Improved access to medicines may also imply marginally lower liability cost for health service providers (resulting in lower insurance premiums).

The following graph summarises the main elements of the cost-benefit model:

Figure 35 Main elements of the cost-benefit model



As an example, we describe one of the main elements of the model, the benefits derived from "avoided lost time by informal carers". To estimate the (social) costs of informal care services required for all more serious cases requiring hospitalisation, we assert that 90% of inpatient cases also require informal care services. Based on the estimate for hospital days mentioned above, it is assumed that in each such case, on average, 9 days are lost. As the monetary value of the informal carer gross salary per year, we use the average value for Germany, which is towards the higher end across the countries covered by the 8 medicines studied here. The benefits are estimated as 20% saved from the cost of the total lost time by informal carers.

The other elements of the model are described in Appendix section E.3

6.2 Cost-benefit assessment of selected medicinal products

6.2.1 Types of medicinal products covered and related ADEs

This analysis represents a bottom-up approach, based on a detailed benefit model and cost data ('economic value') calculated in Chapter 3, and covers eight medicinal products for which sufficient data were available. Seven are for treating a chronic disease and one for an acute disease. They cover a diverse spectrum of seven different diseases. Five of these are used on-label for certain age groups of children, while for three drugs, although PIP studies were negative, data indicate their continued use in children.

Of these eight products, five show low to marginal percentages of all episodes related to paediatrics (0.09%; 0.21%; 0.33%; 0.83%; 1.48% - in absolute numbers: 323; 770; 1,017;

3,209; 4,351). Three have with 7.4%, 9.5% and 37.6% significant shares (absolute: 12,644; 206,986; 405,096).

Making use of FDA and EMA statistics and paediatric safety review reports for the products included, the absolute numbers of ADEs (note: not ADRs, the numbers of which are lower) for the eight drugs were estimated at 0.17, 0.25, 0.87, 1.27, 1.47, 2.00, 4.22, 34.30. The values of serious paediatric ADE reports as percentage of all paediatric episodes, ranging from 0.0002% to 0.41%. Only for a single drug deaths of children were reported as ADEs. Relating those data to a six-month period, an absolute number of 0.25 deaths due to an ADE was estimated. Note that these figures are derived from mathematical computations and therefore are not reported in integers.

In the literature, there is quite some discussion around sometimes significant underreporting of ADRs, ADEs and medication errors. On the other hand, using ADE data leads to overestimation of ADRs. Also, FDA safety reports use prescriptions per patient (sometimes over 10 and more years) as a reference base, which also leads to overestimation of ADEs on a treatment episode base in case the patient obtains more than one prescription during this period. Furthermore, both EMA and FDA note some overreporting (double reports on the same ADE), particularly on deaths, and some error in reporting. For the benefit calculations, the ADE data is adjusted upwards by 100% (doubling) data for deaths, and 200% to 400% (3 to 5 times) for less serious events to account for likely underreporting.

6.2.2 Estimating monopoly rents

To estimate the true costs to national/regional (government) payers and statutory health insurances, monopoly rents as calculated in Chapter 3 for the pharmaceutical industry need to be increased by the extra revenue accruing to other beneficiaries like wholesalers, pharmacies as well governments (wherever VAT or sales tax is levied on medicinal products). In Germany, e.g., this additional monopoly rent amounts to 32% of industry monopoly rent. Because in some countries no wholesalers may be involved or no sales tax is levied on prescription medicinal products, it is assumed that, on average across the EU, the monopoly rent to industry accounts for 87.5% of overall rent, and only 12.5% accrue to other beneficiaries. This renders an extra cost to society estimate of €590m.

In order to arrive at the cost to health system payers (national or regional health services respectively statutory health insurances) this sum needs to be reduced by the (co-)payments charged to patients, respectively their parents. These vary widely across EU member states. We introduced the simple assumption that for each (adult and paediatric) treatment episode the Third-Party Payer receives a lump sum of €5. For the eight medicines overall net extra cost for the 6-month extension is then estimated at €551m to health systems, or more than half a billion Euros. The co-payments by patients of €38.5m are not accounted for as extra costs, because we assume that they may have taken anyhow these or other medicines for which similar co-payments would have to be paid.

This does not hold for one medicinal product. Due to the low price per treatment episode, the full cost of the monopoly rent is allocated solely to patients.

6.2.3 Benefits derived from cash savings due to ADRs avoided

To estimate potential benefits to health systems from cash savings from avoidable ADRs we assumed that they might be reduced by 20% based on estimates in the literature. They will result from hospital stay and outpatient encounters (emergency room visits and ambulatory services) avoided. For the six-month period, the cumulative estimate across all drugs is for avoidable hospitalisation costs €32,000 and outpatient treatment € 5,000, or overall € 37,000 (over a range of €97 to €31,000 per drug). For 10 years, this sums up to € 741,000.

Compared to the overall monopoly rent estimated at more than half a billion Euros, these savings are marginal, leading to benefit-cost ratios of almost zero or a negative return of 99%. Even increasing the estimate for the number of ADEs by another ten times would not lead to any significant results for this item.

6.2.4 Intangible benefits due to ADRs avoided

In a further step, various non-cash or intangible benefits were estimated. They concern benefits expected from improved actual treatment of children, which result in reduced mortality, improved quality of life (QoL) experiences due to long-term disabilities, and time saved by informal carers. Furthermore, in order to account for further benefits not accounted anywhere else, we add a hypothetical benefit of €10 per each treatment episode.

For four medicinal products with very few paediatric treatment episodes compared to all treatment episodes the benefits estimated are considerably higher than for the cash benefits, but still marginal, with less than €100,000 for the 6-month period, and less than €2,000,000 for 10 years. Also the 6-month and 10-year benefit-cost ratios are marginal to negligible.

On the other hand, for the product with the largest share of paediatric treatment episodes the estimated value is very different. We arrived at estimated overall intangible benefits of almost €5m for 6 months, or €100m for ten years. For ten years, we obtained a benefit/cost ratio of 1.5, or a positive rate of return of 50%. For one of the products – the medicine for acute treatment where extra costs accrue only to patients due to higher co-payments, but not to healthcare systems – 10-year intangible benefits are estimated at €80m, leading to a societal benefit/cost ratio of above 5 or a rate of return of more than 400% for this medicinal product.

Overall, the greatest benefits are derived from two rather generic and very rough estimates concerning “avoidable reduced quality of life” and a catch-all “additional benefit per paediatric episode” set at €10. The latter term is used as an estimate of a generic benefit for all due to better treatment options (valued at €5); and in addition, to also account for any other significant ADEs (the number of which is unknown) we apply another €5 per episode. These items are not discussed in the literature, but introduced here to account for any other events and benefits not covered by the earlier items.

Intangible benefits for avoidable reduced quality of life are estimated at €2,840,000 across all medicines (range: €6,120 to €2,470,000); for the ten-year period, the estimate is €56,800,000. This value is directly related to the number of paediatric episodes and the estimated number of serious adverse events, where the Asthma medicine far outstrips all others. Even higher intangible benefits are estimated for the catch-all additional benefit per paediatric episode of €10. Of course, they are directly related to the absolute number of episodes and the percentage of episodes related to paediatrics. Here two drugs are particularly notable: the Asthma medicine with €2,070,000 and the Migraine one with

€4,050,000 for 6 months (the range for other medicines is comparably low: €3,200 to €126,500). The sum across all medicines is €6,340,000 for 6 months and €126,800,000 for 10 years.

Considering the other intangible benefit estimates cumulated across all drugs, deaths avoided do not contribute to a significant extent to the benefits estimated (€360,000 for 6 months or €7,200,000 for 10 years; only one product is involved); this is due to the low number of reports on death events. For intangible costs to informal carers, the total value across all medicines is €9,400 (with individual values ranging from €22 to €8,000) and €188,000 for ten years.

6.2.5 Overall benefit-cost ratio estimate for the eight medicinal products

There are two products (Drug A and Drug B) among the eight medicinal products studied here with strongly favourable benefit-cost ratio when calculated over a 10-year period, basically due to non-cash benefits. Drug A is an Asthma pill and provides €32m net benefit, while Drug B, a migraine pill provides €66m net benefit. All other medicinal products have a negative benefit-cost ratio over 10 years. Aggregating cash and non-cash benefits data for all eight medicinal products, overall benefits of €199m for 10 years are estimated. Overall cash cost to society (patients, health systems) from total monopoly rent to all stakeholders (pharmaceutical industry, wholesalers, pharmacies, governments from value added/sales tax) are estimated at €590m. The overall socio-economic benefit-cost ratio across all medicines is 0.34, the societal overall rate of return minus 66%. A detailed calculation is available in Appendix E.

Table 25 Overview of detailed data estimated and calculated for the benefit-cost estimates per medicinal product

Drug identification letter	**Notes**	**Drug E**	**Drug H**	**Drug F**	**Drug A**	**Drug C**	**Drug B**	**Drug G**	**Drug I**	**Sums / Average**
Indication / diagnosis; pharmaceutical dose form; intake time interval		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Paediatric application		No paediatric dosage recommendations found (intended: [redacted])	No paediatric dosage recommendations found	For children 6 years or older, the recommended dose is 0.7 mg/kg orally once a day.	• 6-14 years of age: one 5-mg chewable tablet • 2-5 years of age: one 4-mg chewable tablet or one sachet of 4-mg oral granules • 12-33 months of age: one sachet of 4-mg oral granules	patients 15 days or older is 150 mg/m2 orally once a day for 14 days followed by a maintenance dose of 150 mg/m2 orally twice a day	• 6 years or older and weight less than 40kg: initial dose of 5 mg orally once • 6 years or older and weight 40kg or greater: initial dose of 10 mg orally once For children, no more than1 dose in any 24-hour period should be given.	For children from 6 to 16 years, an initial dose of 1.3 mg/kg once a day, followed by a maintenance dose of up to 2.7 mg/kg (up to 160 mg) once a day titrated according to patient response.	The safety and efficacy in children and adolescents below 18 years of age have not been established (intended: [redacted])	
No. of countries covered		EU-11	EU-11	EU-10	EU-8	EU-9	EU-9	EU-11	EU 4	
Avoidable	Assumption is that a child that avoids	**-€**	**-€**	**-€**	**360,521 €**	**-€**	**-€**	**-€**	**-€**	**360,521 €**

mortalities (I)	death will live on average another 72 years in "normal" healthy.									
Avoidable hospitalisation cost (II)		**75 €**	**117 €**	**685 €**	**27,231 €**	**1,966 €**	**404 €**	**932 €**	**592 €**	**32,003 €**
Avoidable outpatient treatment (III)		**22 €**	**31 €**	**184 €**	**3,768 €**	**529 €**	**109 €**	**251 €**	**159 €**	**5,053 €**
Avoidable lost time by informal carers (IV)		**22 €**	**34 €**	**201 €**	**7,986 €**	**577 €**	**118 €**	**273 €**	**174 €**	**9,385 €**
Avoidable reduced quality of life (V)		**12,240 €**	**18,000 €**	**105,840 €**	**2,469,319 €**	**303,602 €**	**62,402 €**	**144,000 €**	**91,440 €**	**3,206,844 €**
Sum of additional benefits per paediatric episode (VI)		**32,089 €**	**7,697 €**	**43,509 €**	**2,069,862 €**	**10,173 €**	**4,050,960 €**	**126,440 €**	**3,226 €**	**6,343,957 €**
Total benefits paediatrics (I + II + III + IV + V + VI)		**44,448 €**	**25,880 €**	**150,420 €**	**4,938,687 €**	**316,847 €**	**4,113,994 €**	**271,897 €**	**95,591 €**	**9,957,764 €**
Cash cost - industry monopoly rent - of SPC extension	wholesale based industry revenue	146,496,778 €	31,183,348 €	105,217,160 €	58,121,640 €	9,355,013 €	14,105,120 €	113,220,733 €	39,548,178 €	**517,247,970 €**

Cost - other stakeholders' monopoly rent - of SPC extension	revenue accruing to wholesalers, pharmacies, government(s) (VAT tax) - at an average 14% on industry revenue	20,509,549 €	4,365,669 €	14,730,402 €	8,137,030 €	1,309,702 €	1,974,717 €	15,850,903 €	5,536,745 €	**72,414,716 €**
Total monopoly rent		167,006,327 €	35,549,017 €	119,947,562 €	66,258,670 €	10,664,715 €	16,079,837 €	129,071,636 €	45,084,923 €	**589,662,686 €**
minus revenue from co-payments of patients	Assumption of € 5 per episode, varies greatly across countries	**7,529,141 €**	**1,171,257 €**	**1,469,912 €**	**2,753,208 €**	**53,440 €**	**16,079,837 €**	**7,616,872 €**	**1,832,860 €**	**38,506,528 €**
Net cash cost to healthcare system (statutory insurances or NHS)		**159,477,186 €**	**34,377,760 €**	**118,477,650 €**	**63,505,461 €**	**10,611,275 €**	**-€**	**121,454,764 €**	**43,252,063 €**	**551,156,158 €**
Cash benefits (avoidable hospital, out-patient [ambulatory] costs) (II + III)		97 €	148 €	870 €	31,000 €	2,495 €	513 €	1,183 €	751 €	**37,056 €**
Non-cash (intangible) benefits (avoidable mortality, reduced QoL, informal carers costs + add. benefits per episode) (I + IV + V + VI)		44,351 €	25,732 €	149,550 €	4,907,688 €	314,352 €	4,113,481 €	270,714 €	94,839 €	**9,920,707 €**

6.3 Estimation of cost and benefits medicinal products with compliant PIPs

6.3.1 Introduction

The Paediatric Regulation was a first, most important step ("milestone") to improve the on-label prescribing of medicines for children. However as noted also in other studies, so far only a small start was achieved. As most results from PIPs and other measures are still to come, "however only the children and adolescents of tomorrow" will fully profit.[163] Our estimates attempt to cover this perspective for tomorrow by aggregating estimated benefits over a period of ten years.

Furthermore, planning and executing PIPs and other measures, improving labelling and generating more knowledge on the treatment of children are only "one half of the solution". As long as the second half of the solution is not assured, as long as the new knowledge is not translated into adjusted paediatric prescriptions and clinical practice for better healthcare for children, the overall impact will remain small. Knowledge as such may have intellectual, intangible value in satisfying our curiosity, but as long as it is not diffused and applied in paediatric healthcare provision, it does not generate tangible social or economic value. A basic estimate of such potential benefits is estimated. This estimate remains speculative.

Basis of the following data and 'level 2' calculations of benefits and costs is a list of 119 PIPs[164] which passed the compliance check and were approved by EMA as compliant with the requirements for acceptance. From these, the eight medicinal products covered earlier already obtained the extra 6-month SPC extension and are excluded from the following calculations. This leaves us with 111 PIPs relating to medicinal products. Of these, 21 still qualify for such an extension.[165] The remaining 90 PIPs do not qualify or we do not know their status. 3 of these were excluded due to probable double counting because they relate to the same active ingredient (INN), which leaves us with 87 PIPs for consideration.

6.3.2 Characteristics of drugs covered by PIPs

From a comprehensive German study[166], it is known that the relative distribution of paediatric prescriptions for the top five therapeutic areas (overall about 35.2 m prescriptions for 2011) in Germany is about as follows:

- Pulmonary/ENT diseases: 60%
- Infectious diseases: 22%
- Central nervous system incl. pain: 17%
- Cardiological/heart diseases: 1%
- Oncology: 0.1%

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[163] Afentaki, A. (2014). Arzneimittel für Kinder und „Off-Label-Use" 5 Jahre nach Inkrafttreten der EU-Verordnung (EG) Nr. 1901/2006. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 57(9), p. 1118

[164] Source: EMA. 10-year report on PIPs

[165] This number attempts to exclude double-counting of PIPs for the same drug where we had information on identical active ingredients (INN).

[166] Afentaki, A. op. cit.

Classifying the 108 (87 + 21) PIPs according to these areas plus the categories vaccines and others, we obtain the following results:

- Pulmonary/ENT diseases: 7
- Infectious diseases: 15
- Central nervous system incl. pain: 4
- Cardiological/heart diseases: 6
- Oncology: 7
- Vaccines: 13
- Others: 56

"Others" include therapeutic areas like Dermatology, Diagnostics, Endocrinology-Gynaecology-Fertility-Metabolism, Gastroenterology-Hepatology, Haematology-Hemostaseology, Immunology-Rheumatology-Transplantation, Neonatology-Paediatric Intensive Care, Nutrition, Ophthalmology, Psychiatry, and Uro-Nephrology.

With respect to the type of disease, these can be classified as follows:

- 19 acute
- 9 acute/chronic
- 60 chronic (incl. cancer)
- 13 vaccines
- 7 unknown

Reliable prices for these drugs are difficult to establish. Table 26 presents the ranges estimated based on intensive web searches. *Mutatis mutandis*, it seems that the overall distribution of these PIPs reflects to a great extent the distribution of the eight medicines analysed earlier across these categories.

Table 26 Price range of medicinal products

Price range	**No. of medicinal products**
0.01 – 1.00 €	8
1.01 – 5.00€	15
5.01 -10.00 €	9
10.01 € - 50.00 €	20
> 50.00 €	26
Unknown	30

6.3.3 Estimating future benefits and costs

Except for the benefits and costs estimated in the previous section, we do not have any reliable or meaningful estimates at hand. As a very first and speculative estimate, we apply the following logic for estimating benefits.

The earlier results have shown that cash benefits are in all probability marginal to negligible, so they are not considered. It should be remembered that the most relevant intangible generic benefit for all paediatric patients due to better treatment options was set at €5, and that in addition, to also account for "significant" ADEs (the number of which is unknown), we applied another €5 per episode. Therefore, here we only estimate intangible benefits of a generic kind; but we increase the value per paediatric episode from €10 as used in our earlier estimates to a mean value of €15 to also cover in a cursory manner all other intangible benefits as well.

Due to the severity of oncology incidents with children, we double the estimated benefit per episode to €30. On the other hand, for vaccines we reduce it to €10 to reflect their overall safety and relatively low ADR incidence rate.

The estimates of the paediatric episodes per drug are derived from the estimates per drug for the eight drugs analysed earlier – taking into account the therapeutic indication, plus setting them into some proportion to the overall relevance of the therapeutic area as indicated by the prescribing figures above for Germany. This then allows us to estimate the values presented in the table below.

Table 27 Estimated benefits by therapeutic area

Therapeutic area	No. of PIPs in this area	Estimated paediatric episodes per drug for 10 years	Generic overall intangible benefits in € per episode	Sum of all intangible benefits in €
Pulmonary/ENT diseases	7	1,500,000	15	€ 157,500,000
Infectious diseases	15	500,000	15	€ 112,500,000
Central nervous system incl. pain	4	400,000	15	€ 24,000,000
Cardiological/heart diseases	6	50,000	15	€ 4,500,000
Oncology	7	5,000	30	€ 1,050,000
Vaccines	13	5,000,000	10	€ 650,000,000
Others	56	20,000	15	€ 16,800,000

Therapeutic area	No. of PIPs in this area	Estimated paediatric episodes per drug for 10 years	Generic overall intangible benefits in € per episode	Sum of all intangible benefits in €
Sum				**€ 968,350,000**

6.3.4 Estimating costs to health system payers

Estimating overall cash costs to health system payers is similarly difficult and speculative. It is assumed that of the above PIPs only 21 may be granted an additional 6-month SPC. These cover the following therapeutic fields:

- Pulmonary/ENT diseases: 2
- Infectious diseases: 5
- Cardiological/heart diseases: 4
- Oncology: 1
- Vaccines: 1
- Others: 8

Making use of our earlier estimates for the 8 drugs analysed in the preceding section, we set the extra costs resulting from the 6-month monopoly rent of the marketing authorisation holders at a value of about €50m for the first three therapeutic fields covered by 11 PIPs, and at €20m for the other 10. Then we arrive at an overall estimate of 11 x €50m plus 10 x €20m equal to €750m in monopoly costs.

6.3.5 Summary of results

Comparing these projected first estimates for the 108 extra PIPs, one may contrast the estimated overall intangible benefits of €970m with the estimated extra monopoly costs of €750m. This would lead to a socio-economic benefit-cost ratio of about 1.30 for the 10-year period, or a rate of return of 30% for these additional PIPs.

Adding this "surplus" of €220m to the cash and intangible benefits reported in the previous section, our benefit estimate arrives at roughly €500m. This does not fully cover the estimated monopoly cash cost to health systems estimated there at €590m, but improves the overall balance considerably.

6.4 Estimation of R&D spillovers resulting from the PIPs

Finally, we attempt to estimate the broader socio-economic benefits results from the private sector investment into paediatric R&D (level 1 analysis). The estimation of R&D spillovers is separate from the estimation of the health benefits achieved in relation to new and improved medicine. The positive spillover effects constitute of additional jobs, growth and innovative activity across (EU and non-EU) sectors that would not have happened if it were not for the R&D investment made in relation to the Paediatric Regulation. The investment in R&D, although a cost imposed to the pharmaceutical industry, can also be viewed as an R&D investment towards new and improved medicine that triggers further investment and growth.

This section presents a preliminary analysis of the so-called social rate of return from R&D investment which is equal to the sum of the following:

- Private rate of return to the organisation
- The return to the pharma sector, including to generic companies
- The return to other sectors in the economy

Several studies have estimated rates of return from investment in R&D although the literature in the field of pharmaceutical R&D development is scarce. Annual reporting by GSK (2013, pp. 4 and 2015, p. 4)[167] notes that the estimated internal rate of return of R&D investments is 13% and, in 2013, long-term targets are set at 14%. An earlier study by Garau and Sussex (2007) also refers to a 14% private rate of return[168]. We will use 14% to estimate the private rate of return following € 2,026m investment in R&D (excluding administrative costs, see Chapter 2) in relation to PIPs, see Table 28.

We have not identified estimates of intra-industry and across industry rates of return in the literature specifically related to R&D investment in the pharmaceutical industry. One literature review (Health Economics Research Group and RAND, 2008) summarises the rates of return from different types of R&D investment in different sectors and also provides estimates for the rate of return from UK investment in medical research[169]. The study finds that most literature estimates that the total social rate of return from *private investment* is around 50%, eg 51% as used in Garau and Sussex (2007). Moreover, the study summarises that the total social rate of return from *public investment* is at least 20% and could be as high as 67%, with a more conservative best estimate of 30%. Because the R&D spent in relation to the Paediatric Regulation is an imposed investment rather than a strategic company decision, the 30% rate of social return feels more appropriate than the higher rate of return that is associated with private R&D investment. We assume that the intra-industry and across industry rate of return is equal to the difference between the total social rate of return and the private rate of return and amounts to 16%[170].

It should be noted that in the case of spillovers from private investment in R&D, the literature refers to three types of spillovers: improving the productivity of other firms' R&D, encouraging entry of potential competitors, and a reduction of production costs[171]. In the case of the Paediatric Regulation not all three spillovers may be equally present and the spillover effect might be different in relation investment in paediatric-only trials. Overall, knowledge spillovers are likely to contribute to additional growth and investment.

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[167] http://www.gsk.com/media/325156/annual-report-2013.pdf and http://www.gsk.com/media/1017500/annual-report-2015.pdf

[168] Garau M, Sussex J. Estimating Pharmaceutical Companies' Value to the National Economy. Case study of the British Pharma Group. London: office of Health Economics; 2007.

[169] Frontier Economics (2014). Rates of return to investment in science and innovation, A report prepared for the Department for Business, Innovation and Skills (BIS)

[170] Because of the method of calculating the intra-industry and across industry rate of return and because we have not 'discounted' the 14% rate of return, the private rate of return may also be overestimated and the intra-industry and across industry rate of return may be overstated.

[171] Health Economics Research Group, Office of Health Economics, RAND Europe. Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK. London: UK Evaluation Forum; 2008

Following the study by the Health Economics Research Group and RAND, the above presented rate of return implies that the R&D investment "implies that for an extra €1 invested in cardiovascular research this year, the UK's GDP will be €0.30 higher next year and every year thereafter, than it otherwise would have been" (pp. 40). Based on this estimate, if all of the €2,103m industry spent in relation to the Paediatric Regulation were to yield a 30% social rate of return, that would be equivalent to €608m of GDP every year thereafter.

This degree of perpetuity may be overstated in the case of the Paediatric Regulation and we expect that, in practice, the spillover effect follows a decay curve with an innovation and restructuring phase, following by the diffusion and increase in demand (generics entering the market), and sometime thereafter, a point in time where R&D investment and innovation becomes obsolete. According to a study by Zagame et al (2012), the cumulative effect of an R&D investment can take up to 15 years to accrue but can be preceded by negative rate of return. Following the study, investment benefits from approximately a 10-year period of growth.

For simplicity we assume a linear rate of return with, on average, a total social rate of return of 30% (this is unlikely to be the case and the biggest returns will be experienced in the earlier years) and a maximum cumulative return on investment 10 years after the initial R&D investment. Based on a 30% total social rate of return the total return on investment to society after 10 years amounts to €6,078m and the intra-industry and across industry rate of return after 10 years amounts to €3,242m (see Table 28).

Considering the 10-year period, both the private and intra-industry and across industry rates of return are larger than the initial investment suggesting a healthy return.

The economic value of the SPC extension was estimated (extrapolated based on actual data) for 12 products that accrued economic value until 2015 for relevant EU member states to amount to €742k. The estimated social return is significantly higher than this economic value of the SPC extension (excluding cost to society in relation to other products and countries, as well as the dead weight loss in relation to the SPC). Despite the crude methodology used to estimate the effect of spillovers and the challenge to gross up the value of the direct loss to society as a result of the Paediatric Regulation (ie the reward to industry), it suggests that the benefits of the Regulation outweigh the costs.

Table 28 Estimated rate of return to society of the Paediatric Regulation, in € millions

	Private rate of return	**Intra-industry and across industry rate of return**		**Total social return**	
Estimated rate of return from € 2,026 investment in R&D		**From private investment**	**From public investment (preferred estimate)**	**From private investment**	**From public investment (preferred estimate)**
	14%	37%	16%	51%	30%

Estimated rate of return from € 2,026 investment in R&D	Private rate of return	Intra-industry and across industry rate of return		Total social return	
		From private investment	From public investment (preferred estimate)	From private investment	From public investment (preferred estimate)
After 1 year	€ 284	€ 750	€ 324	€ 1,033	€ 608
After 2 years	€ 567	€ 1,499	€ 648	€ 2,067	€ 1,216
After 5 years	€ 1,418	€ 3,748	€ 1,621	€ 5,166	€ 3,039
After 10 years	€ 2,836	€ 7,496	€ 3,242	€ 10,333	€ 6,078

Estimated total R&D costs of PIPs for the industry per year (2008-2015) was estimated at €2,026m, excluding administrative costs, see Chapter 2.

7 Summary and conclusions

The current study is aimed at providing a review of the economic impacts of the Regulation since it entered into force. This study thus covers the following dimensions:

- Analysis of the regulatory costs to the pharmaceutical industry for meeting the legal obligations
- Analysis of the economic value of the rewards/ incentives to the pharmaceutical industry
- Overall assessment of the rewards/ incentives to the pharmaceutical industry
- Analysis of the direct and indirect social and economic benefits
- Exploratory high-level cost-benefit assessment providing estimates of the broad economic impacts

The regulatory costs analysis aimed to capture and assess all the costs incurred by the sponsors of paediatric clinical trials within the scope of Paediatric Investigation Plans (PIPs). Cost estimates were based on a consultation of PIP and waiver applicants by means of a survey questionnaire and follow-up interviews. The total cost of the Paediatric Regulation incurred to industry is estimated to be €2,106m per year or €16,848m for the years 2008-2015. The annual cost estimate includes €2,103m PIP-related compliance costs and €3.6m costs for waiver applications. On average, the estimated costs made in relation to in-vitro studies and animal studies and the development of a paediatric formulation are relatively lower than the costs of Phase II and Phase III paediatric clinical trials, and some of the other R&D costs incurred in relation to the PIP, such as pharmacokinetics and pharmacodynamics studies. The variation in cost is also dependent on the number of modifications to the PIP, the number of clinical studies, the number of paediatric subjects, the duration of the PIP, and therapeutic area.

The analysis of the economic value of the rewards and incentives provided under the Paediatric Regulation - in relation to the six-month SPC extension (article 36), the Orphan reward (article 37) and the PUMA reward (article 38) - is based on a methodological framework that considers the additional period of protection (from competition with generic medicines) that is awarded to originator companies. Moreover, because the introduction of generic medicines is delayed, society does not benefit from increased competition and lower prices for the duration of the exclusivity extension and this effect is also accounted for in the framework.

The analysis on SPC extensions covers 8 medicinal products which received SPC extensions in the period between 2007-2012 and lost their exclusivity before the third quarter of 2014. The analysis, based on available data from IMS Health, shows that there are significant differences between products and countries. The data analysis shows that the price drop of branded products often starts in the first quarter after the loss of exclusivity, this price drop is often limited in scale (up to 10-20%). During the first and second year after the loss of exclusivity, the branded prices decrease further, and there are significant differences between products and countries. In stabilised market situations, the economic value as a percentage of 6-month revenue varies between 11% and 94%. The combined economic value (or monopoly

rent) of the 8 products is calculated to amount to €517m. The economic value was then extrapolated in order to assess the magnitude of the 'full' economic value of the reward up to December 2015. This includes an extrapolation of the economic value of the products studied in detail to countries where SPC extension was granted but our datasets did not include those geographies. In addition, the economic value of a further four products (with SPC extension ending within the research period) was estimated based on the average economic value per capita. The extrapolated economic value thus amounts to €926m between 2007-2015.

There are four products with Orphan reward to date that may be studied but since these are still under protection it was not possible to estimate the economic value of the reward. Projection of currently available data towards the loss of exclusivity in the future is unreliable. However, the approach to estimate the economic value of Orphan rewards could, in principle, be similar to the model used for the SPC extension, with the main difference being the delay of two years rather than 6 months.

There are only two PUMAs that were authorised up to December 2015. Given the limitations of the available data, it is not possible to project the economic value of these PUMA rewards. There is however a fundamental difference with respect to estimating the SPC reward: market exclusivity period for a product starts at the moment the PUMA reward is granted instead of after a delay as for the SPC-extension. This implies that the 'economic value' covers the 'monopoly benefits' a product receives from additional data exclusivity (8 years) and market protection (2 years). A model was developed that could be applied in future studies.

An assessment of the rewards to industry is based on five specific evaluation criteria: relevance, effectiveness, efficiency, coherence, and utility/potential for improvement. We collected data through a survey to pharmaceutical companies, which was complemented with interviews and desk research. The objectives of the reward scheme are deemed highly relevant when considering that the rewards provide a way for organisations to sponsor and support the development of paediatric medicines. Nevertheless, the rewards themselves cannot guarantee capital allocation decisions that maximise value for companies or result in positive return on investment in individual R&D programmes.

The Regulation and hence the combination of obligations and rewards is seen as effective to shift focus to paediatric medicine development. As a result, the amount and quality of research and information available for the paediatric population has already increased. Over the period between 2007-2015, the share of paediatric trials among all clinical trials increased 2.5-fold and over 100 PIPs were completed. Paediatric clinical research networks have been set up involving academia and industry. Industry also changed their approach to medicine development and now design their research and development plans incorporating the paediatric population. The Regulation is considered as a commendable first step in the right direction but there remain therapeutic areas where significant unmet need continues to exist, such as in the field of paediatric oncology, and hence further steps and more time is needed to achieve the expected impact. It is claimed that therapeutic areas covered by research in children is driven mainly by commercial interest and reflecting the needs of the adults rather than those of children.

It is noted that the effectiveness of the rewards is higher for high-volume products and lower for indications with very limited patient numbers. Factors influencing effectiveness include uncertainty (and discontinuity) in early product development, difficulty in recruitment of

paediatric subjects, compliance check procedures, and the time-limited nature and complexity of obtaining the reward across member states once the clinical research is completed.

The extent to which rewards were taken up by companies indicate that the 6-month SPC extension is the main tool to incentivise and reward paediatric medicine development. The effectiveness of the orphan and the PUMA rewards are not immediately obvious with very few examples in the period 2007-2015. External factors, such as the continued off-label use of cheaper and comparable medicinal products represents a disincentive for paediatric medicine development. The lack of meaningful market exclusivity and unpredictable return on investment (due to pricing and reimbursement practices) in a niche market makes it difficult for PUMA to act as a strong incentive. The development of orphan drugs targeting children is complex and costly with very small study populations. Nevertheless, stakeholders consider the orphan designation as a strong incentive and expect to see an increase in orphan rewards in the coming years. One of the drawbacks highlighted was the lack of choice for companies between the orphan designation and SPC extension if the substance is also registered for non-orphan indication.

Industrial stakeholders indicate that the PIP application and administrative procedures consume significant resources. This would be seen as unattractive for smaller companies. This is despite the fact that a more streamlined process is in place since 2014 and mandatory "key binding elements" of a PIP are defined and thus the need for minor PIP modifications are decreased. Further, engaging with the regulatory system is often found to be slow, fragmented across different committees, thus resulting in additional costs and delays in product development.

There are a number of initiatives in member states which are complementary to or extending the implementation of the Regulation. For example, priority review of paediatric data and clinical trial applications in member states aimed to provide accelerated access to paediatric medicinal products. In addition, national legislation is available in some cases to reduce the off-label use of medicines for children or to use financial incentives to encourage the use of paediatric medicine. Paediatric research networks with industry/academia participation have also been created and supported at the national level. Nevertheless, there is scope for enhancing research collaboration through the mobilisation of EU research funds.

Public stakeholders indicate that the Regulation was set up from an overly narrow perspective, excluding considerations for affordability, cost-effectiveness and budget implications at the national level. From the public perspective, the effectiveness of the Regulation may be viewed as somewhat reduced because public services may ultimately decide not to pay for the registered paediatric medicines. The fact that the entry of generic medicine to market is blocked for 6 months represents a high price to pay for a branded product. Generic companies would consider important that SPC extension can only be granted to the company that sponsors a paediatric study and is responsible for the compliance with the PIP (market authorisation holder), not to other third parties.

The legislation in the US differs in various ways from the EU Regulation. Although not mandated by legislation, the US has set up and funds the Paediatric Trials Network (enabled by the Best Pharmaceuticals for Children Act, BPCA) that, with over 100 clinical sites, conducts paediatric clinical trials and generates paediatric data on products. BPCA also

provides a financial incentive (6-month market exclusivity) to companies to voluntarily conduct paediatric studies under a Pediatric Written Request (WR). These WRs are issued based on a priority list, representing a balanced portfolio of therapeutic areas and paediatric needs, without replicating research funded elsewhere. The Pediatric Research Equity Act (PREA) on the other hand is mandatory and requires an initial Paediatric Study Plan (PSP) at the end of Phase II. The EMA and FDA collaborate within the framework of the international Paediatric Cluster to exchange information, agree on scientific requirements and harmonise requests to sponsors. A current special initiative is the Pediatric Rare Disease Priority Review Voucher awarded upon approval of a new product application for rare paediatric disease indications. This is a transferable voucher for sponsors to obtain a priority review of any subsequent drug application. However, there is no legislation to address the challenge of new drug development when no adult indication exists.

CA consultation on the societal benefits of the Paediatric Regulation was conducted through a two stage survey (Delphi) to expert stakeholders. This survey reveals a broadly positive view of the regulation's effect on medicines development. The majority of the respondents agree or strongly agree that the number of paediatric research projects increased, that more quality information is available on approved medicines for their use in paediatric population, and that the awareness of health professionals for better evaluation of medicine for children has increased. 84% of respondents indicate that there has been a measurable increase in the numbers of medicines tested within paediatric populations in the period since the implementation of the regulation. The survey revealed a broadly positive view about improving research capacity and research collaboration, with a somewhat more neutral view expressed about any improving trends in paediatric research funding. Regarding the replacing of existing treatments for a paediatric condition (either by treatment with less toxicity or enhanced efficacy), close to half of the respondents find that the regulation had led to an increase. While 68% of the respondents find that there has been an increase in the number of children treated with the right medicine at the right time with the right dose. Almost 40% of respondents indicate they have seen improvements in child morbidity in their field, which they would attribute to the regulation, which is encouraging at this point in time. Moreover, the majority of stakeholders expect that the regulation will have measurable long-term benefits, eg improving children's school attendance, reducing time cares need to take off work to care for children, increasing quality-adjusted life years for children, and decreasing mortality rates of children with life-threatening illnesses. Positive societal benefits were also reported as part of the survey to industry, eg it was reported that the Paediatric Regulation evoked a change in culture and a significant shift in mind-set and helped encourage paediatric development become a more integral part of the overall development of medicines in Europe.

The Paediatric Regulation is expected to have a positive impact on improved treatment for children and is expected to contribute to a reduction of adverse drug reactions. This in return is expected to improve the quality of life of children, avoid mortalities, hospitalisation costs, ambulatory costs, lost time by informal carers, and is expected to lead to other improvements related to better treatment for children. The (exploratory) cost-benefit analysis seeks to contrast these benefits with the cost to society resulting from the extra monopoly rent obtained by the sponsors of PIPs as a result of the Paediatric Regulation.

There are two products (Drug A and drug B) among the eight medicinal products studied here with strongly favourable benefit-cost ratio when calculated over a 10-year period, basically due to non-cash benefits. Drug A is an Asthma pill and provides €32m net benefit, while Drug B, a migraine pill provides €66m net benefit. All other medicinal products have a negative benefit-cost ratio over 10 years. Based on the aggregation of cash and non-cash benefits data for eight medicinal products, it is estimated that these eight products yield overall benefits of €199m over a period of 10 years. Overall cash cost to society (patients, health systems) from total monopoly rent to all stakeholders (pharmaceutical industry, wholesalers, pharmacies, governments from value added/sales tax) were estimated at €590m. As a result, the overall socio-economic benefit cost ratio across these medicines is 0.34, the societal overall rate of return minus 66%. It is expected that those PIPs that have already received a positive statement of compliance but are not (yet) received a reward, on average, also have a positive effect on society resulting from the change in labelling/safer medicine. Based on an exploratory extrapolation of cost and benefits that may exist in relation to 108 of such additional PIPs, the benefit estimate arrives at around €500m, which is close to the estimated value of monopoly rents.

The investment in R&D made in relation to the PIPs, although a cost imposed on the pharmaceutical industry, can also be viewed as an R&D investment towards new and improved medicine that triggers further investment and contributes to the creation of jobs, growth and innovative activity across (EU and non-EU) sectors. These so-called spillover effects are estimated based on rates of return that are documented in related literature. The more conservative estimated rate of return from an annual €2bn investment in R&D could, after a period of 10 years, yield a total social return of around €6bn. This estimated social return is significantly higher than the value of the SPC extension (excluding cost to society in relation to other products and countries, as well as the dead weight loss in relation to the SPC) suggesting that, in monetary terms, the benefits of the Paediatric Regulation outweigh the costs

Appendix A Regulatory cost data and analysis

A.1 Scope of the survey to industry

We designed a survey to PIP and waiver applicants inquiring about the specific cost elements related to paediatric drug development. The relevant costs include all of the following internal and outsourced costs that have been completed to date:

- Administrative costs of a PIP / waiver application
- R&D costs:
  - Cost incurred in relation to in-vitro studies and animal studies for paediatric indications
  - Cost incurred in relation to the development of a paediatric formulation
  - Cost incurred in relation to phase II paediatric clinical
  - Cost incurred in relation to phase III paediatric clinical trials
  - Other costs incurred in relation to completing a paediatric investigation plan (eg, modelling and simulation/ extrapolation studies, data management costs, coordination costs)
  - Cost incurred or expected in future in relation to long-term safety and efficacy monitoring after marketing authorisation

The survey excluded costs incurred in relation to marketing, legal costs of SPC extension (these costs will be estimated in a separate study issued by the European Commission), and manufacturing/distribution costs. The survey additionally asked PIP applicants to indicate:

- Collaborations with a research network (eg the European Network of Paediatric Research at the European Medicines Agency) in relation to completing a paediatric investigation plan
- Estimated benefit resulting from the scientific advice received from EMA (ie reduced costs incurred)
- Whether the applicant filed or is planning to file an application to the FDA in the USA using the information generated by the PIP
- A set of open-ended questions about the relevance, effectiveness, efficiency, coherence and utility of the paediatric regulation

A.2 Survey design process

In reference to the tender specification, we prepared a draft cost data questionnaire. This draft was improved in several stages. First, during the inception phase of the study, we received a number of comments from the steering group that were used to modify the first draft of the cost data questionnaire.

We conducted a first pilot of the questionnaire with representatives of one pharmaceutical company (Merck Group). We shared our draft data questionnaire and discussed it in detail in a follow-up telephone meeting.

We then conducted a second pilot with EFPIA member companies (coordinated by EFPIA Regulatory Affairs division) to which we submitted our improved data questionnaire. The study team received written comments on the questionnaire from over 10 companies and discussed these comments in a teleconference with EFPIA and member organisations. The main points discussed included the following:

- The commercially sensitive nature of the information requested
- Feasibility to complete the data provision
- Relevance of costs resulting from the Paediatric Regulation other than costs related to PIP
- Planned timeline
- Underlying cost drivers of PIPs and the degree of representativeness

Following the teleconference with EFPIA and EFPIA member organisations, the study team consulted with DG SANTE and EMA and updated the data questionnaire using the feedback received. As described below, several modifications to the design were incorporated.

- The information requested from companies is commercially sensitive. Therefore we communicated to the companies invited to partake that:
  - All data received is treated in strict confidence and, as registered data manager under the UK Data Protection Act 1998,
  - We have established processes to ensure the security of the data and information that we collect and hold.
  - Only aggregate data will be part of our reports to the European Commission and will not be attributed to individual companies.
  - If necessary, bilateral confidentiality agreements can be agreed upon (which a handful of companies have taken up).
- Because companies with a large number of PIP and waiver applications were concerned about the feasibility to complete all data provision the study team looked into ways to reduce the data request by capping the data request to individual companies to maximum 10 PIP/waiver applications. Companies that have 3-10 applications were requested to provide information on all applications.
- Other major cost items linked to paediatric medicine development, ie legal costs linked to SPC extension, HTA requirements, medicine manufacturing and distribution costs were agreed not to be in scope for this study. (Note that the review of SPC legislation will be the subject of a separate EC study). Costs associated with long-term safety and efficacy monitoring is however deemed within scope to evaluate the overall impact on the development costs of paediatric medicines and thus a separate survey question is now included for these costs.
- The proposed 3-week data collection period was judged too short to collect relevant data from various company departments internally. In order to avoid unnecessary delays, we maintained a 3-4 week deadline in our official invitation but have agreed to a more flexible deadline whenever companies indicated that more time was needed to complete the survey. This extension of deadline was thought to apply mostly to the companies that have submitted 10 PIPs or more. In reality the data collection process extended over several months.

- Consideration of cost drivers is carried forward in the design of the sampling frame

A.3 Design of sample population

The total number of PIP/waiver applications with decisions dates for the years 2007-2015 is 1,297. We used web-scraping to download the data from the EMA website. This data was cleaned and structured to identify the company names and e-mail addresses of all applicants that have applied to EMA for three or more PIPs or waivers. This resulted in the selection of 78 companies and this group submitted an estimated number of 870 PIP applications/waiver applications. The total number of applications requested per company was however capped at a maximum of 10 for practical reasons (see above). Nevertheless, companies that submitted more than 10 applications were invited to submit data on additional PIPs. The capping of applications resulted in a target sample population of 514 applications, 40% of the total population.

Table 29 Population and target sample population of PIP/waiver applications

Population	Target population	Target population as a percentage of total population
1,297	514	40%

A total of 26 companies applied for more than 10 PIP/waiver applications. We pre-selected the applications requested from this group of companies on the basis of four criteria to maintain representativeness of the sample and avoid the arbitrariness of companies 'cherry-picking' their PIPs. In order to collect data on cost incurred in relation to phase II and phase III paediatric clinical trials, preference was given to PIPs that received a compliance check (hence providing more complete data set). In the total population 94 PIPs had received a final compliance check. The target population of PIPs with a compliance check is 82, or 89% of the total population.

Table 30 Population and target sample population of PIP/waiver applications which received a final compliance check

Population	Target population	Target population as a percentage of total population
94	82	87%

Our sampling frame also uses the following criteria:

- Decision year – the sample should be representative of the costs incurred over the time-frame, we use decision year as a proxy
- Decision type – the cost of the Regulation is expected to differ between application types
- Therapeutic area – conducting clinical trials in some therapeutic areas is thought to be costlier than in others.

A.3.1 Submitting the survey

The pre-populated survey was sent by e-mail to 78 companies on the 8th of February. The survey was sent and addressed to the contact(s) most commonly listed in reference to the PIP on the website of EMA. We screened the e-mails and sought to identify alternative e-mail addresses whenever the e-mail address was no longer in use. Sometimes the e-mail address was a generic e-mail address of a company and sometimes a personalised e-mail address. Additional contacts from EFPIA were put in copy. A covering e-mail provided a succinct overview of the study objectives and attached to the e-mail were the prepopulated questionnaire and the letter confirming the validity of this study from DG SANTE. The companies invited to partake were asked to confirm receipt of the e-mail and were asked to return the completed survey by 3 March. Using the same survey template 18 EU Framework Programme participants that were likely to have submitted a PIP were approached and asked to contribute to the data collection. Companies were offered a prolonged deadline of 31 March 2016, which lapsed and we received the last submissions in mid-June.

A.3.2 Response rates

Out of the 78 invitations sent to companies 19 companies returned cost data on PIP/waivers, although not always for the complete set of PIPs/waivers for which we had requested data. We were notified that in some cases PIPs requested concerned products that had been transferred from the target company and were no longer part of the company product portfolio. In another cases companies merged or split since the PIP application date.

Given our target sample population of 514 PIP/waiver applications (excluding FP7 participants that altogether only submitted a small number of PIPs), we have a response rate of 24%, which is relatively high for this type of exercise, especially considering the difficulty to retrieve this type of data retrospectively. Given the total population of 1,297 applications this is a sample size of 9%.

Table 31 Target sample population and response rates of PIP/waiver applications

Target population	**Sample population**	**Response rate, given total number of applications included in the data request**
514	121	24%

Table 32 Population and response rates of PIP/waiver applications

Population	**Sample population**	**Proportion of the total number of applications**
1,297	121	9%

Table 33 Population and target sample population of PIP applications which received a final compliance check

Population	Sample population	Proportion of the total number of applications
94	17	18%

In reference to the sampling frame we observe the following:

- Decision year - see Figure 36– the distribution of the sample by decisions year is roughly aligned with the distribution for the overall population of PIPs. There exists a slight undersampling for the year 2010 and a light oversampling for the year 2014. Although our data request is limited to costs incurred over the period 2008-2015, in practice a small number of PIPs were registered to have had a modification in 2016 and this latest reference date is reported below (this is not expected to have influenced cost estimations).
- Decision type – see Figure 37 –we compare the number of decisions agreeing on a PIP relative to the number of decisions related to applications for modification of our sample and the population. We find that there is a slight oversampling of decisions related to application for modifications – which is related to the fact that there is a small number of PIPs that were registered as not having any agreed modifications at the time the data was downloaded that resulted in having had a modification at the time of data provision. We expect this slight oversampling to not be of major concern although it could slightly inflate some of the administrative costs related to filing a PIP.
- Therapeutic area – see Figure 38 - the distribution of the sample by therapeutic area is roughly aligned with that of the sample population (based on data from the EMA 10 year report) and more data was collected on the therapeutic areas for which a relatively larger number of PIPs was submitted: eg Endocrinology, -gynaecology-fertility-metabolism, Haematology-Hemostaseology, Oncology, Immunology-Rheumatology-Transplantation, and Infectious diseases. Relatively fewer data was collected in the 'other' category'

Figure 36 Distribution of PIPs for sample and population, by decision year

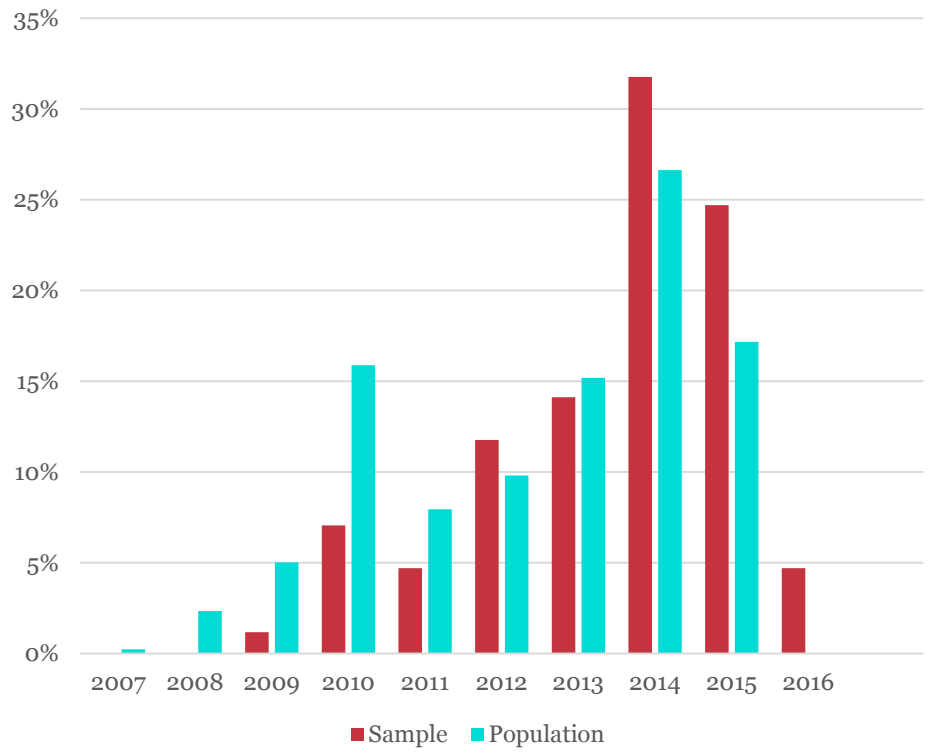


Figure 37 Distribution of PIPs for sample and population, by decision type

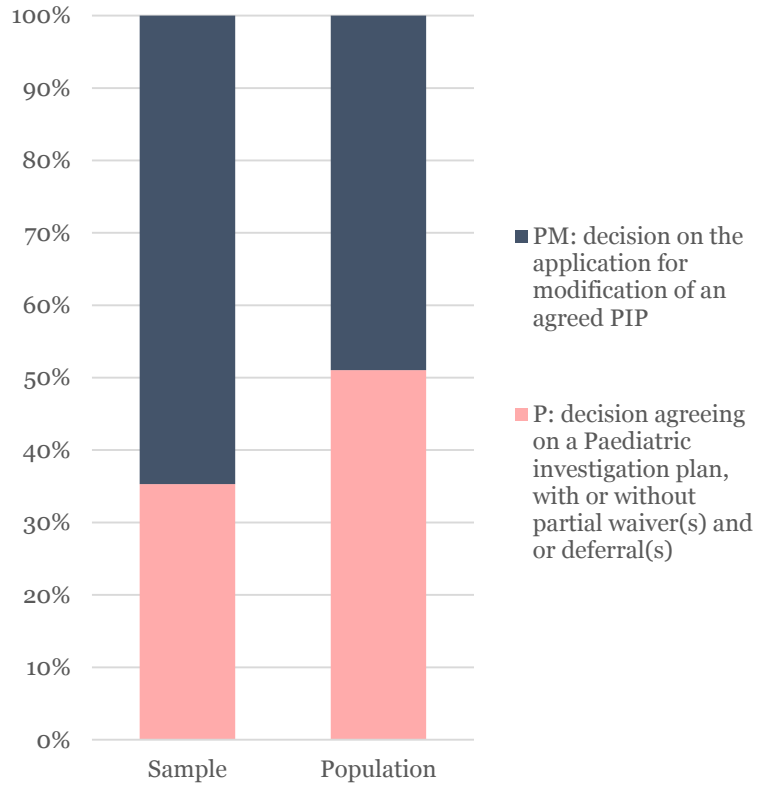
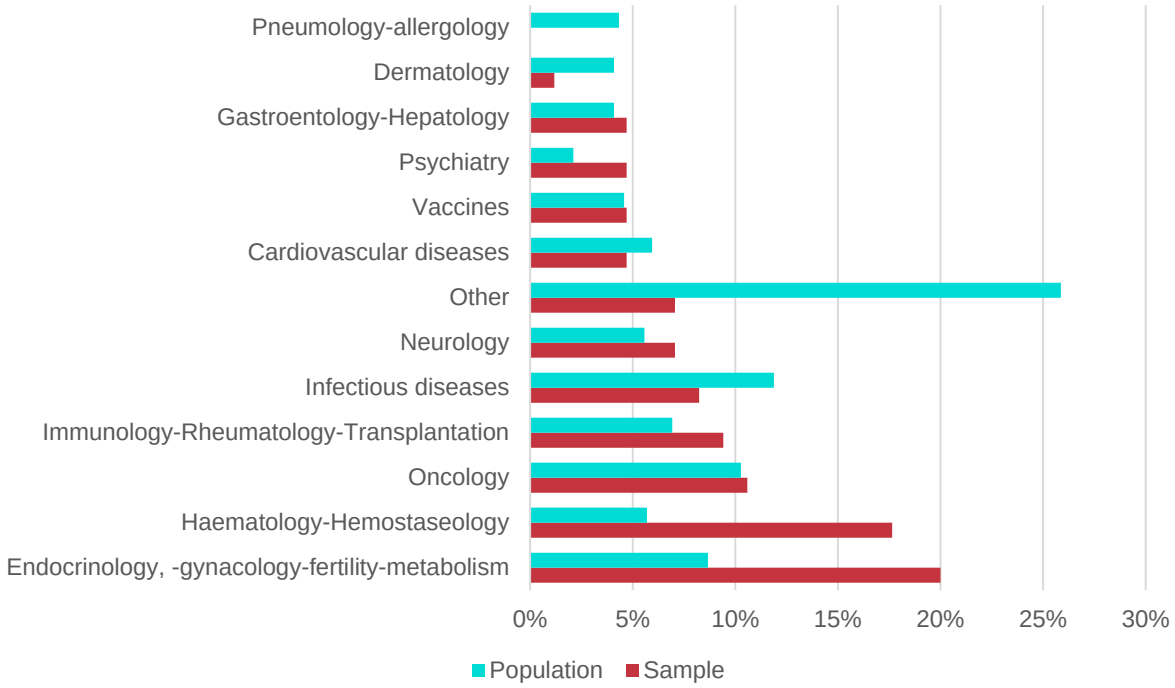


Figure 38 Distribution of PIPs for sample and population, by therapeutic area



Source: data on the population is from the EMA 10-year report

A.4 Data treatment and scaling up costs

For each of the organisation from which we have collected data we set up a process of clarification/follow-up and (re-)formatting before entering cost data into an aggregate database. This included a process of carefully distinguishing between 'missing data' (where the companies were unable to provide response) and denoting cases where no costs were incurred.

For the administrative costs some data was collected on estimated total number of hours spent. As part of our cleaning process, the associated cost per hour was verified to be in line with expectations. Although there are differences in the FTE rates in relation to function and year as well as salary differences across EU member states, no abnormalities in the data were detected.

Table 34 presents an overview of the data collected on PIPs. Although we collected data 85 PIPs, in some instances organisations were unable to report cost data for each of the various phases. Also, some organisations did not incur any cost for a specific phase (because the phase was not a requirement of the PIP) and this is taken into account as part of the approach to scale-up.

Estimating the cost to industry involves several steps. First data is aggregated for each PIP phase. This yields an estimate cost figure for costs incurred during 2008-2015 for the sample.

Next, this estimate cost figure is weighted by multiplying the average cost incurred for our sample by the total number of initial PIP decisions made over the period 2008-2015, which is 858 (or 107.3 on average per year)[172]. Gross estimates are divided by 8 and presented as annual estimated cost figures.

A similar approach is used to scale-up cost to industry in relation to waivers, however, in this case we refer to the total number of full waivers granted during 2008-2015 which is 403 (or 50.4 on average per year)[173].

Average and median cost figures for each phase are calculated based on only the sub-set of data that reflect a complete (R&D) phase[174].

Table 34 Overview of data on PIPs

	Percentage of PIPs for which organisations reported to have incurred costs	**Percentage of PIPs with completed phase**
Labour cost incurred for preparation of the initial application	85% (72)	100%
Labour cost of annual reporting and further PIP modifications	46% (39)	100%
Other costs incurred in relation to preparing and modifying an application	38% (32)	100%
In-vitro studies and animal studies	31% (26)	81%
Development of a paediatric formulation	36% (31)	45%
Phase II paediatric clinical trials	35% (30)	60%
Phase III paediatric clinical trials	55% (47)	43%
Other R&D costs incurred in relation to completing a paediatric investigation plan	42% (36)	-

[172] EMA 10 year report

[173] EMA 10 year report

[174] The robustness of the estimate of total cost to industry is verified by scaling-up the average cost estimates using the total number of initial PIP submissions for 2008-2015 and accounting for the probability of PIPs entering a given phase (based on organizations reporting of whether a cost was incurred or not). Using this alternative approach to scaling-up the average R&D costs are €22m rather than €19m, which is fairly close. The later cost estimate is considered more robust because it builds on a larger sample.

Study on the economic impact of the Paediatric Regulation - including its rewards and incentives

The Technopolis Group, in partnership with empirica and Ecorys Nederland, has been commissioned by DG SANTE to provide a comprehensive and independent review of the economic impacts of the Paediatric Regulation since it entered into force in January 2007

Background of the study
The Paediatric Regulation was enacted in the European Union in 2007 to encourage development of suitable medicine for children, promote high quality research, improve the information available on the use of medicines in children and to prioritise the therapeutic needs in this group. This is to be achieved via a set of rewards and incentives for both new/on-patent products, and off-patent products, with an additional set of tools for transparency, information and research stimulation. In 2013 the Commission published a progress report on the first five years of application of the Paediatric Regulation. In 2017 the Commission is due to provide a further report on the impact of the Paediatric Regulation, which will include an analysis of the economic impact of the rewards and incentives.

Objective of the study
The main objective of this study is to evaluate the economic impact of the Paediatric Regulation. This includes an assessment of the costs that companies incur in order to comply with the obligations under the Paediatric Regulation.

In order to collect data on the regulatory cost to industry, we are consulting PIP and waiver applicants through this questionnaire.
Please complete the data request as detailed in the next tab of this speadsheet labelled "FORM"

Please return the questionnaire by the 3rd of March 2016 by email to: paediatric-study@technopolis-group.com

Data treatment
We have requested information on estimated costs incurred. Costs may be rounded to the nearest €1,000
We will treat all data received in strict confidence and, as registered data manager under the UK Data Protection Act 1998, we have established processes to ensure the security of the data and information that we collect and hold. Only aggregate data will be part of our reports to the European Commission and will not be attributed to individual companies. Please let us know if you require bilateral confidentiality agreement to be signed with Technopolis.

We thank you in advance for your contribution; your participation is very much appreciated, as it is especially important to the robustness and success of the study for the European Commission.

If you have any question regarding this inquiry, please contact the project manager, Dr Peter Varnai, Principal Life Sciences and Health at Technopolis Group by email peter.varnai@technopolis-group.com or telephone +44 1273 204320. If you would like to obtain additional information about the study, please contact Florian Schmidt at DG SANTE Medicinal products, by email Florian.Schmidt@ec.europa.eu or by telephone +32 229 52327.

Please note the following before providing data:
We are aware that multiple clinical trials may be linked to a given PIP and clinical trials are often carried out in mixed populations (adult and paediatric). This survey aims to capture only the specific cost related to paediatric drug development.

Please provide total costs for each item including internal and outsourced costs for each category.
Please include costs incurred in relation to a completed or partially completed phase.
Please do not include costs incurred in relation to:
- Marketing costs
- Legal costs of SPC extension (these costs will be estimated in a seperated study issued by the European Commission)
- Manufacturing/distribution costs

Survey of the costs incurred related to Paediatric Regulations

Please complete all cells highlighted in yellow

Company name:				
E-mail:				
SME (YES/NO)		**PIP 1**	**PIP 2**	**PIP 3**
	Initial application year			
	Decision year			
	Application number			
	Decision (eg P, PM, W)			
	Therapeutic area (s)			
	Please indicate the number of clinical studies agreed in this PIP			
	Current PIP stage: 1. Not started 2. Ongoing 3. Discontinued 4. Completed (final compliance check)			
	Paediatric product stage: 1. Under development 2. Application for marketing authorisation submitted 3. Marketing authorisation in EU obtained 4. Marketed in at least one EU member state 5. Discontinued			
	Adminsitrative costs of a PIP / waiver application			
Q1 Labour cost incurred for preparation of the intial application (include both internal and outsourced costs)	Estimated costs (EUR)	€ 0	€ 0	€ 0
Labour cost of annual reporting and further PIP modifications	Estimated costs (EUR)	€ 0	€ 0	€ 0
	Estimated total number of hours spent	0	0	0
Q2 Other costs incurred in relation to preparing and modifying an application	Estimated costs (EUR)	€ 0	€ 0	€ 0
	Estimated total number of hours spent	0	0	0
	Please specify			

R&D costs

Q3	Cost incurred in relation to in-vitro studies and animal studies for paediatric indications	Estimated costs (EUR)	€ 0	€ 0	€ 0
		Phase completed (yes/no)			
Q4	Cost incurred in relation to the development of a paediatric formulation (please exclude costs indicated under Q3)	Estimated costs (EUR)	€ 0	€ 0	€ 0
		Phase completed (yes/no)			
Q5	Cost incurred in relation to phase II paediatric clinical trials (please exclude costs indicated under Q3)	Estimated costs (EUR)	€ 0	€ 0	€ 0
		Phase completed (yes/no)			
	Total number of paediatric trial subjects participated in the phase II clinical trial(s)	Number (estimate)	0	0	0
		Please estimate the number of EU paediatric trial subjects involved in this phase	0	0	0
Q6	Cost incurred in relation to phase III paediatric clinical trials (please exclude costs indicated under Q3)	Estimated costs (EUR)	€ 0	€ 0	€ 0
		Phase completed (yes/no)			
	Total number of paediatric subjects participated in the phase III clinical trial(s)	Number (estimate)	0	0	0
		Please estimate the number of EU paediatric trial subjects involved in this phase	0	0	0
Q7	Other costs incurred in relation to completing a paediatric investigation plan (eg, modelling and simulation/ extrapolation studies, data management costs, coordination costs)	Estimated costs (EUR)	€ 0	€ 0	€ 0
		Please specify			
Q8	Have you collaborated with a research network (eg the European Network of Paediatric Research at the European Medicines Agency) in relation to completing a paediatric investigation plan?	Please specify (yes/no)			
		Comments			
Q9	Cost incurred or expected in future in relation to long-term safety and efficacy monitoring after marketing authorisation	Estimated annual costs (EUR)	€ 0	€ 0	€ 0
		Expected duration (Years)			
Q10	Estimated benefit resulting from the scientific advice received from EMA (ie reduced costs incurred)	Estimated monetised benefit (EUR)	€ 0	€ 0	€ 0
		Comments			
Q11	Have you filed or are you planning to file an application to the FDA in the USA using the information generated by this PIP?	Please specify (yes/no)			
		Comments			

Please provide your opinions and views about the Paediatric Regulation by responding the following questions:

	The Paediatric Regulation aims to: 1. Facilitate the development and accessibility of medicinal products for use in the paediatric population 2. Ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population 3. Improve the information available on the use of medicinal products in the various paediatric populations	
Q12	Are the objectives of the rewards provided by the Regulation relevant to your needs and objectives? Not relevant / Somewhat relevant / Highly relevant. Please explain	
	In your view, how effective are the rewards as a mechanism and means to achieve the objectives of the Paediatric Regulation? Not effective / Somewhat effective / Highly effective. Please explain	
	What measures (if any) could be taken to improve the effectiveness of the rewards in obtaining the above-mentioned objectives?	
	What aspects of the rewards are the most efficient or inefficient according to you (in terms of the investments to obtain a reward with respect to its benefits)? For example, rewards linked to off-label products (PUMA).	
	Please share with us any lessons that can be drawn from the implementation of the rewards? How are these useful for current or future activities to be taken by the Commission and/or other stakeholders?	
	To the best of your knowledge, are there any overlaps and complementarities between the rewards and any other EU Member State action in paediatric medicine development?	
	Please provide any example of societal benefits resulting from the Paediatric Regulation (eg, support to research institutes/ increased capacity in paediatric medicine, better health in children)	
	In your view, are there any lessons to be learnt from the rewards provided under the US paediatric legislation (ie, pediatric voucher)?	
	is there anything else you would like to add or comment upon?	

Please provide follow-up contact information below:

	Name
For follow-up clarifications, please provide your contact information:	
	email
	telephone number

Definitions

Labour cost	Labour costs incurred estimated on a full economic cost (FEC) basis
Decision types	P: decision agreeing on a Paediatric investigation plan, with or without partial waiver(s) and or deferral(s) W: decision granting a waiver in all age groups for the listed condition(s) PM: decision on the application for modification of an agreed PIP RP: decision refers to a refusal on a proposed Paediatric Investigation Plan RW: decision refers to a refusal on a request for waiver in all age groups for the listed condition(s) RPM: decision refers to a refusal on the application for modification of an agreed PIP
Phase II clinical trials	Studies conducted to evaluate the efficacy and safety of the medicine
Phase III clinical trial	Studies conducted after the efficacy is demonstrated and prior to the approval and launch of the drug
Long-term safety and efficacy monitoring	Studies conducted after marketing authorisation has been granted, including pharmacovigilance

Average yearly exchange rates from Euro (EUR)

	Bulgarian lev	Swiss franc	Czech koruna	Danish krone	British pound sterling	Croatian kuna	Hungarian forint	Polish zloty	Romanian leu	Swedish krona	US dollar
Year	BGN	CHF	CZK	DKK	GBP	HRK	HUF	PLN	ROL	SEK	USD
2007	1.961	1.643	7.782	7.451	0.685	7.348	2.052	3.793	0.522	9.253	1.371
2008	1.959	1.587	4.990	7.457	0.796	7.239	2.433	3.523	1.885	9.627	1.471
2009	1.958	1.510	6.478	7.447	0.892	7.356	1.151	4.337	1.259	0.629	1.395
2010	1.958	1.383	5.321	7.448	0.859	7.306	5.935	4.003	5.539	9.556	1.328
2011	1.957	1.234	4.610	7.451	0.868	7.456	9.961	4.126	7.054	9.036	1.393
2012	1.959	1.205	5.162	7.444	0.811	7.539	9.851	4.189	5.720	8.711	1.286
2013	1.959	1.231	5.988	7.458	0.849	7.589	7.191	4.199	2.833	8.656	1.328
2014	1.959	1.215	7.555	7.455	0.807	7.640	8.885	4.189	1.882	9.103	1.329
2015	1.960	1.069	7.308	7.459	0.727	7.620	0.260	4.188	7.374	9.366	1.111

Appendix B Insights from literature with regard to the economic value of the Regulation

Although the availability of literature on the 'economic value' of the Regulation is limited, the key principles described above can be found in publications which focus on the US and the EU.

The US paediatric regulation[175] was introduced in 1994 and asked developers to screen the availability and quality of paediatric data in order to complement the information on the labels. In 1997, the Food and Drug Administration Modernization Act (FDAMA) introduced a six-month SPC extension (the 'Paediatric Exclusivity Provision') for products with paediatric data: a developer had to submit a written request to get this extension, even if the data did not prove the safety and efficacy of paediatric use. Since 2003 the legislation requires paediatric assessments for all new medicinal products (active ingredients, dosages etc.).[176, 177]

There are three studies about the economic impact of the six-month SPC prolongation in the US. In 2012, Nelson et al. studied the economic impact (from a payer perspective) of the patent extensions in statins, ace inhibitors and selective serotonin reuptake inhibitors (SSRI).[178] The authors linked the economic impact to the cost for society due to the delayed generic market entry.

Nelson estimated the economic impact on the Utah Medicaid drug programme at $2.2m and on all the Medicaid programmes in the US at $430m.[179] The decrease of reimbursement cost after exclusivity expiration per product was estimated at 3.8% to 24.4% within 18 month after the expiration date of the original patent.[180] In 2008, Baker-Smith et al already conducted a similar analysis.[181] The latter author calculated the 'rate of economic return to cost'. This is a comparison of the net return during and after the (additional) six-month marketing exclusivity period. [182] Baker-Smith observed that there was a big variation between the economic returns (and costs) of 9 orally administered anti-hypertensive drugs (from 1997 until 2004). The main conclusion of this study was that the Paediatric Exclusivity Provision "has generated highly variable, yet lucrative returns to industry sponsors". This is mainly

[175] Final Rule 59 FR 64242.

[176] FDA. 2013. Guidance for Industry and Review Staff: Paediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (good review practice).

[177] Hoppu et al. 2012. 'The status of paediatric medicines initiatives around the world- what has happened and what has not?' *European Journal of Clinical Pharmacology* 68 p. 1-10.

[178] Nelson et al 2011. Patent extension policy for paediatric indications: an evaluation of the impact within three drug classes in a state Medicaid programme, Applied Health Economic Health Policy. 2011 May 1;9(3):171-81.

[179] Note that the Medicaid programme is a joint federal and state programme that covers medical costs for people with limited income and resources in the US. The Medicaid programme does, however, not reimburse all medical costs. (Source: https://www.medicare.gov/your-medicare-costs/help-paying-costs/medicaid/medicaid.html).

[180] The total costs of the six-month SPC prolongation were based on an assessment of 14 different medicines (divided in three classes) over a period of 18 months after original patent expiration date.

[181] Baker-Smith. 2008. The economic returns of paediatric clinical trials of antihypertensive drugs.

[182] Explanation: Estimates of net economic return per drug were calculated based upon cash outflows and cash inflows adjusted to their 2005 values. Net return-to-investment ratios were calculated to reflect 6 months of marketing exclusivity by averaging cash inflows over 3 years to obtain an estimate of average annual cash inflow and dividing this value by 2 to obtain a 6-monthestimate.

caused by large sale volumes, while the medicinal product is still under protection. The 'rate of economic return to cost' varied between 4 and 65. The study of Li[183], which used the same approach, likewise resulted in the same conclusions, only with a broader representation of the paediatric exclusivity program (more different indications). This study shows a rate of economic return to cost from (minus) –1 to 74.

Literature which assesses the European situation is scarce. Medicines for Europe published in 2012 a position paper in which they (amongst others) estimate the 'costs' of the SPC extension: the SPC extension results in a six-month delay of the price fall, which can be expected after the loss of patent exclusivity.[184] Medicines for Europe claims that the SPC extension resulted in 2012 in approximate €2.3bn loss of savings for European healthcare systems.

With regard to pharmaceuticals in general, the sector enquiry of DG COMP (2009) analysed the functioning of the pharmaceutical market and examined the reasons for observed delays in the entry of generic medicines to the market and the apparent decline in innovation.[185] The sector enquiry did not assess the 'economic value' of the relevant exclusivity rights, but focused on the effect of delays in the market entry of generic medicinal products. In the econometric analysis DG COMP assessed the post-entry change in the average price level and the generic producers' market share. Three important elements were (amongst others) taken into account. First, the change in average drug prices at the end of the sample relative to the price level prior to loss of exclusivity. This 'price drop' is calculated for the long-run and for specific periods (1-4 years after the loss of exclusivity). Second, this should be combined with the time it takes a generic product to enter the market (time to entry). Third, the share of generic producers, after the loss of exclusivity (in comparison with the share of the originators). In fact, this represents the market penetration of the generic product.

DG COMP confirmed that, due to several factors, there exists a delay of generic market entry. For the sample of medicines studied in the inquiry the average time to enter the market (after loss of exclusivity) was more than seven months. For the most selling medicines it took about four months. With regard to the price drop, DG COMP observed that the price of generic medicines during the first year after loss of exclusivity was, on average, 25% lower than the price of the originator medicines (prior to the loss of exclusivity). Two years after entry, prices of generic medicines were on average 40% below the former originator price. In terms of market share (volume), DG COMP saw that the share of generic companies was approximately 30% after one year and 45% after two years. Medicines for Europe indicated that, compared to the sector enquiry in 2009, the pressure on generic prices increased (e.g. due to mandatory price cuts).[186]

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[183] J. S. Li. 2007. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program

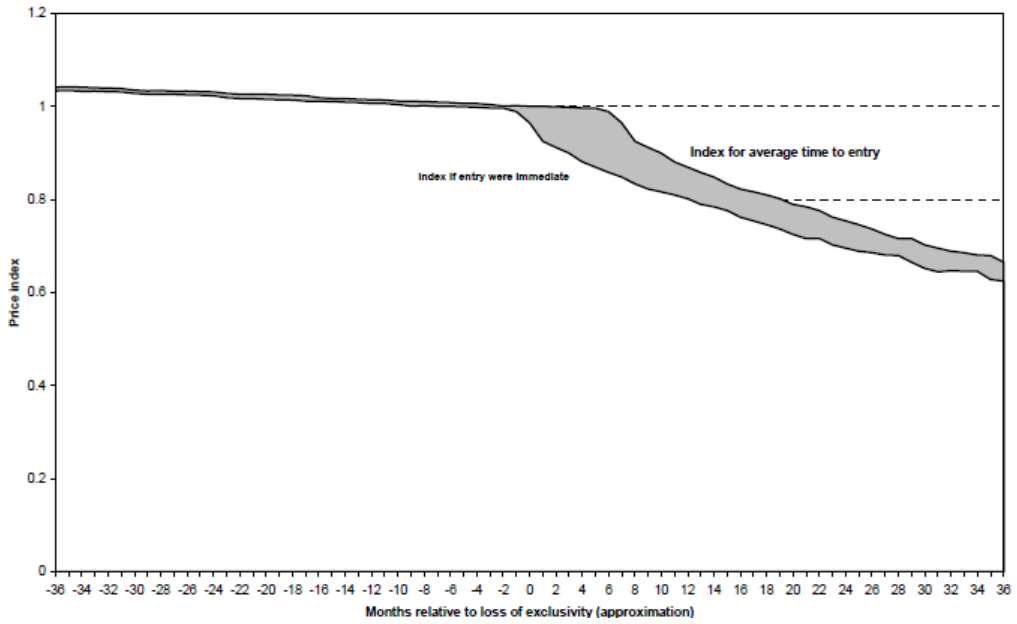
[184] European Generic Medicines Association, 'EGA contribution to EC public consultation on general Report on experience acquired as a result of the Application of the Paediatric Regulation', November 2012.

[185] European Commission, DG COMP. 2009. Sector enquiry of the pharmaceutical market. See: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/.

[186] European Commission, DG COMP. 2009. Sector enquiry of the pharmaceutical market. See final report, consideration 1556-1560.

With regard to the methodological framework for this study, the analysis of DG COMP of the potential savings for society is of particular interest. They assessed the potential savings that might be realised if generic medicines enter the market immediately after the loss of exclusivity (instead of the average time to enter of seven month). This is illustrated by the grey area in the Figure below.

Figure 39 Potential savings in case of immediate generic entry



DG COMP. 2009. Sector enquiry of the pharmaceutical market. Final report, consideration 216-217

In the analysis, DG COMP shifted the actual curve ('*index for average time to entr*') seven month to the left ('*index if entry was immediate*') and estimated the difference between the curves, which represents the potential savings for society.

Appendix C Reward data, limitations and analyses

C.1 Data used in the analysis

C.1.1 Structure of the dataset

Through a third party agreement with the European Commission and the Intercontinental Marketing Services Health (IMS Health), the project team obtained relevant data for this study. This dataset contains quarterly sales and volume data (i.e. revenues and units sold). The variables together enabled the calculation of price per unit. The dataset contained data from the 1st quarter of 2008 until the 3rd quarter of 2014.

The table below shows the six categories available within the dataset. The first category is the International non-proprietary name (INN), which is the globally recognised way of naming pharmaceutical active substances.[187] The second category contains the countries in which the INN is sold, distinguishing between sales distributed through hospital and retail. When there is no distinction between hospital and retail data, this category is coded as 'combined'. The third category is the company which sells the specific product. This company can be the manufacturer with the marketing authorisation, the parallel import company or the national distributor. The fourth category is the brand name of the product. Each INN can enclose several brand names. Each branded product contains the same active substance (cat. 1). Besides this active substance, a branded product can contain other pharmaceutical substances. The fifth category covers the type of product, i.e. non-generic or generic product. When the type of product is unknown, this category is coded as 'uncategorised'. The sixth category contains the product characteristics, covering the specific route of administration, the dosage and the package size.

Table 35 Categories available in IMS Health data

Category	Description
1.	International non-proprietary name (INN)
2.	Country
3.	Company
4.	Brand
5.	Type of product
6.	Package/dose

[187] World Health Organization. Guidelines International non-proprietary name (INN). Available at: http://www.who.int/medicines/services/inn/en/

We obtained data for 22 products to calculate the economic value and the secondary outcomes of the corresponding awards: 14 products with a six-month supplementary protection certificate (SPC) extension, 6 products with an Orphan Designation and an approved Paediatric Investigation Plan and, 2 products with a Paediatric-Use Marketing Authorisation Plan (PUMA). We selected the 22 products based on the yearly reports of European Commission (2007-2015)[188] and expert opinion. The specific countries per product for which we requested data are specified in the table below.

C.2 Data limitations

The datasets obtained did not fully comprise the requested data in terms of product and country coverage. The limitations stated below are thus the limitations of the dataset, not of the methodology of the analysis. The latter will be discussed in the next section.

C.2.1 Product limitations (category 1)

The selection of products and countries was based on the year in which the award was granted.[189] This year is not the same year as the year in which the patent extension starts. This additional protection starts when the 'basic' protection ends. Therefore, some products had to be excluded, because the date of patent expiry was outside the timeframe of the dataset (Q1 2008-Q3 2014).

Out of the 22 requested products, 14 products were excluded: 5 products with an SPC extension, all (6) products with an Orphan Designation and an approved PIP and, all (2) products with PUMA were excluded.

Beside these 14 excluded products, we excluded Drug D. For this drug the data did not allow distinction between protected and non-protected products by the SPC extension. The month of the patent expiry of the SPC extension was August 2013. However, the data showed generic entries from 2008 and onwards. These generic products are products with an alternate salt,[190] and were therefore allowed to enter the market. In the dataset obtained, the salts used in Drug D products were not identifiable. Therefore, we excluded this product from further analysis.

C.2.2 Country limitations (category 2)

Since a patent extension has to be granted by the national authority, the geographical coverage differs per product (see Table 2). Not all marketing authorisation holders request patent extensions in all countries. The countries in which they requested patent extensions are listed in the column 'countries requested'. However, not all countries were present in the datasets obtained. For example, no data were available for Cyprus, Malta, Denmark, Iceland and Liechtenstein. Only partial (retail turnover only) data were available for the Netherlands,

[188] European Commission. Medicinal products for human use. Medicines for Children. Available at: http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm

[189] European Commission. Medicinal products for human use. Medicines for Children. Available at: http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm

[190] INN insight, available at: http://www.genericsweb.com/index.php?object_id=XXX

Latvia, Greece, Luxembourg and Estonia. Combined data only were available for Slovenia (note that combined data means that there is no distinction between hospital and retail data).

C.2.3 Type of product limitations (category 5)

This study focussed on the entry of generic products and the effects of these entries. Therefore, it was important that distinction is made between non-generic and generic products in each country as key variables. For Luxembourg and Slovenia, there was no such distinction made and, for this reason, data from these two countries were excluded from further analysis.

C.2.4 Package/dosage limitations (category 6)

The dataset obtained did not contain specific Defined Daily Dose (DDD) information. DDD is a standardised measure of medicine use per day. The dataset however contained all available dosages and package sizes on the market and, as a result, we could consider comparable dosages by converting the size of the package into comparable single units. Extrapolations were then made to the entire dataset (see below).

Table 36 Availability/limitations of data

#	INN	Brand name	Award	Countries requested	Missing countries	Date of patent expiry	In-cluded	Counties with limitations
1	Infliximab	Remicade	SPC	Sweden, Italy, France	Denmark, Luxembourg, The Netherlands	February 2015	No	N/A
2	Insulin	Lantus	SPC	Italy, Sweden, Ireland	Denmark	May 2015	No	N/A
3	Etanercept	Enbrel	SPC	France, Sweden, Ireland, Italy	The Netherlands	August 2015	No	N/A
4	Abatacept	Orencia	SPC	Germany, France, Austria, Luxembourg, Italy, UK, Ireland, Sweden, Finland, Portugal, Romania,	Denmark, Estonia, Slovenia, The Netherlands, Bulgaria	December 2017	No	N/A
5	Caspofungin	Cancidas	SPC	Italy, UK, Austria, Ireland, Romania, Slovenia, Greece, Netherlands, Germany, France, Belgium, Finland, Portugal, Sweden,	Denmark	April 2017	No	N/A
6	Nevirapine	Viramune	SPC	Belgium, Germany, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK	Denmark	July 2013	Yes	Netherlands (retail only) Luxembourg (uncategorised)
7	Zoledronic Acid	Zometa a.a.n.	SPC	Austria, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Portugal, Romania, Slovenia, Sweden, UK	Denmark	May 2013	Yes	Netherlands (retail only) Luxembourg and Slovenia (uncategorised)
8	Rizatriptan	Maxalt	SPC	Belgium, France, Germany, Italy, Luxembourg, Netherlands, Spain, Sweden, UK	Denmark , Ireland	August 2013	Yes	Netherlands (retail only) Luxembourg (uncategorised)
9	Latanoprost	Xalatan	SPC	Austria, Finland, Germany, Ireland, Italy, Luxembourg, Netherlands,	Denmark	January 2012	Yes	Netherlands (retail only)

#	INN	Brand name	Award	Countries requested	Missing countries	Date of patent expiry	In-cluded	Counties with limitations
				Portugal, Sweden, UK				Luxembourg (uncategorised)
10	Anastrazole	Arimidex	SPC	Austria, Belgium, Finland, France,, Germany, Ireland, Italy, Luxembourg, Netherlands, Sweden, UK	Denmark	February 2011	Yes	Netherlands (retail only) Luxembourg (uncategorised)
11	Montelukast	Singulair	SPC	Germany, Ireland, , Italy, Luxembourg, Netherlands, Slovenia, Spain, Sweden	Denmark	February 2013	Yes	Netherlands (retail only) Luxembourg and Slovenia (uncategorised)
12	Clopidogrel	Plavix	SPC	Italy, Germany, Spain, Finland, Ireland, Sweden, Portugal, Belgium	Denmark	August 2013	Yes	Expiry dates in countries differ from expected expiry date.
13	Losartan	Cozaar	SPC	Austria, Belgium, Finland, France, Germany, Ireland, , Italy, Netherlands, Sweden, UK,	Denmark	March 2010	Yes	No
14	Valsartan	Diovan	SPC	Austria, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Portugal, Sweden, UK	Denmark	November 2011	Yes	Netherlands (retail only) Luxembourg (uncategorised)
15	Anagrelide	Xagrid	Orphan	France, Finland, Greece, Norway, Belgium, Luxembourg, Sweden, Estonia, Romania, Hungary	Denmark		No	N/A
16	Eculizumab	Soliris	Orphan	Belgium, France	Denmark, Finland, Greece, Hungary, Luxembourg, The Netherlands, Romania, Slovenia		No	N/A
17	Sapropterin	Kuvan	Orphan	Belgium, Czech Republic, Estonia, France, Greece, Hungary, The Netherlands	Denmark, Latvia, Luxembourg, Slovakia		No	N/A

#	INN	Brand name	Award	Countries requested	Missing countries	Date of patent expiry	In-cluded	Counties with limitations
18	Tobramycin	Tobi Podahler	Orphan	France, Czech Republic, Finland, Luxembourg, Estonia, Bulgaria, Slovakia, Netherlands, Sweden, Slovenia	Denmark		No	N/A
19	Midazolam	Buccolam	PUMA	France, UK, Ireland, Germany, Italy, Spain, Finland, Sweden, Greece	Denmark		No	N/A
20	Propranolol	Hemangiol	PUMA	France, Portugal, Sweden, Austria, Netherlands, Germany, Spain, Romania, Slovenia	Denmark		No	N/A

C.3 Data cleaning

C.3.1 Data check

Before data cleaning, each data category was checked for irregularities. A checklist regarding these irregularities in the data can be found below.

Table 37 Data checklist

Category	Description	Check
1.	INN	- Check if there is one active substance
2.	Country	- Check which countries are included - Check if the countries contain hospital and retail data.
3.	Manufacturer	- Check if the manufacturer of the non-generic product is the same as the company to whom the reward is granted
4.	Brand	- Mark other products with independent market authorisations, which are not protected by the SPC/Orphan/PUMA-extension.
5.	Type of product	- Check if there are uncategorised products, besides the non-generic and generic products
6.	Package: dose	- Check how many different packages/doses are presented. Highlight different products/characteristics.

C.3.2 Data cleaning

The following steps were taken to prepare the data for analysis:

1. Mark (label) the quarter in which the patents expires
2. Exclude products with independent market authorisations, not protected by SPC extension (category 4)
3. Exclude non-categorised products (category 5)
4. Make an overview of the different packages/dosages (category 6)
5. Exclude packages/dosages with a different route of administration (not protected by the SPC extension) (category 6)
6. Sum the quarterly revenues of every different dosage. Create percentages of these quarterly sums, divided by the total of the dataset, minus excluded products.
7. Select most sold dosage
8. Highlight the different sizes of the packages
9. Extract revenue and volume of the packages of the selected dosage ranked on country and generic/non-generic
10. Convert different sizes of the packages into single units (e.g. the volume of a package of 60 pieces has to be multiplied by 60)
11. Create totals of the revenues of all the non-generic/generic products and the overall total
12. Create totals of the volumes of all the non-generic/generic products and the overall total

Regarding step 6, the coverage of the selected products is presented below. We found that in 5 products the coverage of the most sold dosage is higher than 70%. In the three other products this coverage is lower than 70%. However, there is no way to increase this percentage, because these products do have more than one product which is frequently sold.

Table 38 Coverage selected products in the dataset (EU-level)

INN	Minimum	Maximum	Difference	Mean	C.I. 95%
Drug E	74.6%	89.5%	14.9%	82.8%	2.7%
Drug D	81.9%	99.8%	17.8%	90.5%	3.7%
Drug H	88.3%	99.5%	11.2%	97.6%	1.8%
Drug F	55.2%	64.6%	9.3%	59.4%	1.4%
Drug A	58.1%	78.3%	20.2%	67.1%	3.0%
Drug C	78.5%	91.4%	12.8%	83.9%	2.0%
Drug B	71.7%	76.1%	4.4%	74.1%	0.6%
Drug G	28.3%	41.1%	12.8%	33.3%	2.6%
Drug I	50.9%	70.4%	19.6%	65.8%	3.1%

The characteristics of the included products are presented below. We present the therapeutic area of the indication of the product, the excluded brands (step 2) and packages (step 5), the selected product with the highest revenue share (step 7) and the maximum sales per quarter.

Table 39 Characteristics of the 8 products considered in this study

INN	Therapeutic area	Excluded products	Most sold dose	Included /packages	Max. sales per quarter
Drug E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug H	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

INN	Therapeutic area	Excluded products	Most sold dose	Included /packages	Max. sales per quarter
Drug G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C.4 Assumptions

To clean and prepare the data for analysis, we had to make some assumptions. The two assumptions, related to selection of the most sold dosage and converting the different package sizes, are stated below:

1. Selecting the most sold dosage should be based on the coverage of the total revenues.
   - Explanation: the most important coverage is the percentage of the revenues and not of the volumes. Because when small package is sold many times, it does not have a big impact on the revenues. The average coverage should be covering the total revenue with 70% (see Table 38)
2. The price per single unit is not dependent on the size of the package.
   - Explanation: the packages of the most sold dosage are converted into single units (e.g. one tablet). Converting the size of packages into single units is feasible and accountable. This is proven by the comparison of price/unit for different package sizes.

C.5 Limitations due to data cleaning

Due to the selection of the most sold dosage, the less sold dosages were excluded from the analyses. Ideally, the most sold product covers the hospital and retail data, and non-generic and generic products per country. For some products one of these four variables could not be covered, due to the selection of the most sold dosage, see table below.

Table 40 Limitations due to selection of most sold dosage

Product	Country	Limitation
Drug B	Belgium	Only non-generic products
Drug I	Ireland	Only generic products
Drug I	Italy	Only generic products
Drug I	Romania	Only generic products
Drug I	Finland	No products
Drug I	Austria	Data gap

Product	Country	Limitation
Drug C	Sweden	Only non-generic products

C.6 Methodology of data analysis

In this section, the methodology of the data analysis is presented for the five relevant aspects: generic entry, time between patent expiring and entry of generic, price- and volume effects, substitution effects and the economic value of the rewards.

C.6.1 Generic entry

From the 1st quarter of 2008 until the 3rd quarter of 2014, the number of generic products are extracted. The two selection criteria for extraction were labelled as generic product in the dataset and a registered volume higher than zero. After the extraction, the number of generic entries in the quarters after the patent expiry were counted and presented in tables.

In the dataset, a non-generic product was sometimes labelled as generic product (especially in the data from the Netherlands). These products were manually traced and corrected; these products could be found in two ways: entering the market before the patent expiry and a relatively high price compared to the other generics.

C.6.2 Time-to-event data

Due to quarterly data, the first generic entry happened for (almost) all products in the first quarter after the loss of exclusivity. Therefore, the time to entry was zero in most of the cases.

When the data is suitable for time-to-event analyses, we used survival analysis. With this type of analysis, the duration from the beginning of the observation until the event happens could be measured. The censored events are also included in this analysis. These analyses result in a probability of generic entry after time *t*.

C.6.3 Price- and volume effects

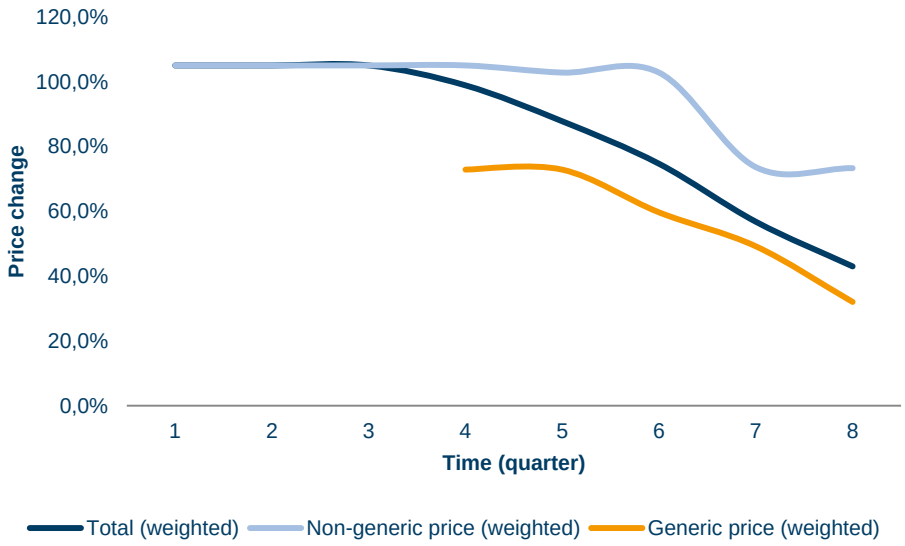
Price- and volume effects are presented as a result of generic entry. The dataset contained only revenue and volume data.

After converting the different packages per dosage volume per single unit, the price was calculated. The revenues per quarter per product divided by the volume per unit results in the price per single unit. Note that the prices derived from the dataset were not corrected for inflation.

The next step is to go from prices per single product to average price per category (non-generic, generic product). The average price per category was not calculated based on the individual prices. For these prices, the total revenue per category was divided by the total volume in single units per category. This method corrects for volume differences, the so called weighted prices. Besides the weighted prices per category, the weighted overall prices were also calculated. This overall price showed the extent to which the market is served by non-generic and generic products. The share of the generic products is reflected in the weighted total prices. An example of these weighted prices is presented in the figure below.

When the total (weighted) line is moving to the generic (weighted) line, the generic share of the total volume is increasing.

Figure 40 Example of changes in weighted prices



Presentation of absolute prices, besides the issue of confidentiality, is often not easy to read and certainly not easy to interpret. The calculated prices per category and the total prices are converted into index prices. The first price available in the dataset (1st quarter of 2008 in most cases) is the reference price. The index prices of the total weighted prices and the weighted non-generic prices per products are based on the first available prices of the corresponding category. However, index prices of the weighted generic prices are based on the first available price of the weighted non-generic prices. The index prices of the generic products are relative to the price of the non-generic products.

Due to the use of index prices, the average price changes per product are easy to read and interpret. Subsequently, the price drop is calculated, based on the index prices.

Volume data was available in the dataset. After extracting the non-generic and generic products of the most sold dosage and after converting the packages of different sizes into single units, the market share of both categories was calculated. The market share is presented as percentages. Percentages facilitate the comparison of market share between products.

The methods described in the previous sections enabled us to calculate:

- Price drop (long run): percent drop between the price before the loss of exclusivity and the price in the 3rd quarter of 2014
- Price drop per year: percent drop between the price before the loss of exclusivity and the price at 1, 2, 3 and 4 year(s) after first generic entry
- Generic market share (long run): volume share of generics in the 3rd quarter of 2014

- Generic market share per year: volume share of generics in 1st, 2nd, 3rd and 4th year after first generic entry

C.7 Substitution effects

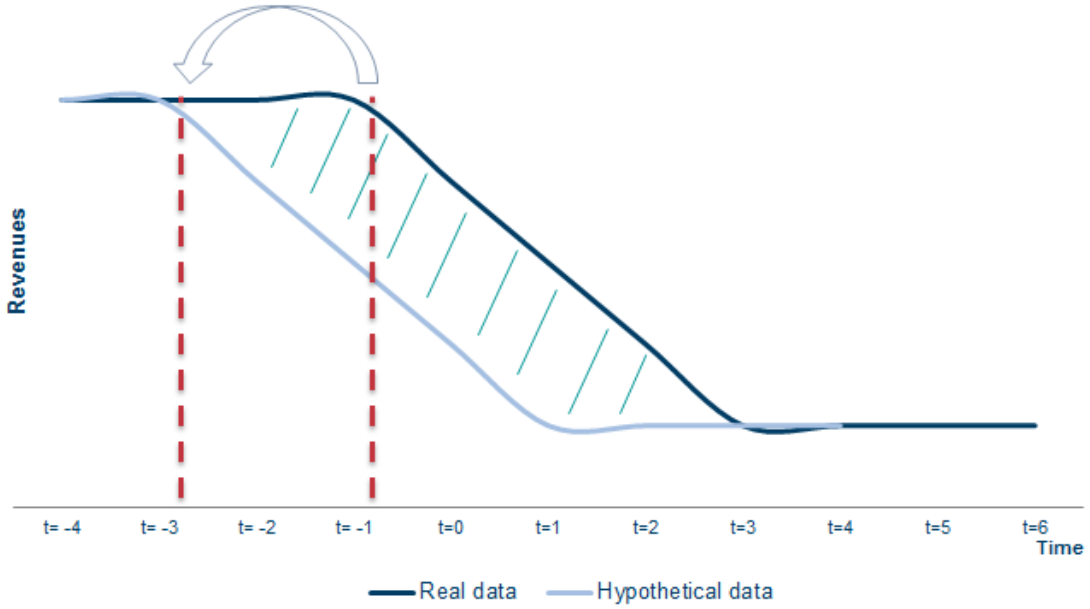
Substitution effects can occur for products with the same active substance or for products with other active substances within the same therapeutic class. These effects are identified by evaluating the total volume of the product. Index numbers of the volumes were created. The reference volume of these index numbers was the first available volume in the dataset, the 1st quarter of 2008 in most cases. Subsequently, the volume changes (in percentages) were calculated, based on the index numbers of the volume. When the volume was decreasing with more than 20%, there could be a substitution effect. However, the dataset we analysed did not include data of other active substances within the same therapeutic class. Therefore, the occurrence of a substitution effect was determined by literature review and patent research.

In case of the Orphan reward, this effect is unlikely, due to niche market of these paediatric drugs.

C.8 Methodology to calculate the economic value of SPC extension

In order to calculate the economic value of the SPC extension reward, we make use of the real data (revenues) that covers the time when the SPC extension occurred and generate hypothetical data to describe a situation without SPC extension. The total revenue of calculated with SPC extension minus the total revenue calculated without SPC extension is the actual *economic value* of the SPC extension reward (shaded area in the figure below).

Figure 41 Model used to calculate the economic value of the SPC extension



t= time in quarters (3 months)

C.8.1 Real situation (with SPC extension)

This situation uses the available sales data to calculate actual revenues. The total revenue in this situation covers the period from two quarters before the SPC extension expiry (t= -2) until the revenue stabilises after the SPC extension. The quarter in which the SPC extension expires, is labelled as t=0.

From the dataset it can be derived that stabilisation of the revenue for the products studied occurs sometime between t=2 to t=6. Note that for example when the stabilisation occurs in t=3, the period from expiry to stabilisation takes 1 year (t=0 -> t=3). Stabilisation is dependent on the time delay between SPC expiry and entry of generics, which is distinct in each country (related to external factors such as drug policy, drug prescribing patterns, etc.).

C.8.2 Hypothetical situation (without SPC extension)

This situation is based on hypothetical data when the product would not benefit from SPC extension. The total revenue in this situation covers the period from the quarter of the SPC extension expiry (t= 0) until the budget stabilises after the SPC extension plus 2 quarters. The length of this time period should be the same compared to the real situation. In this hypothetical situation, the revenue of the product of the first two selected quarters should be lower compared to the revenue of the product of the first two selected quarters in the real situation, because of the earlier patent expiry.

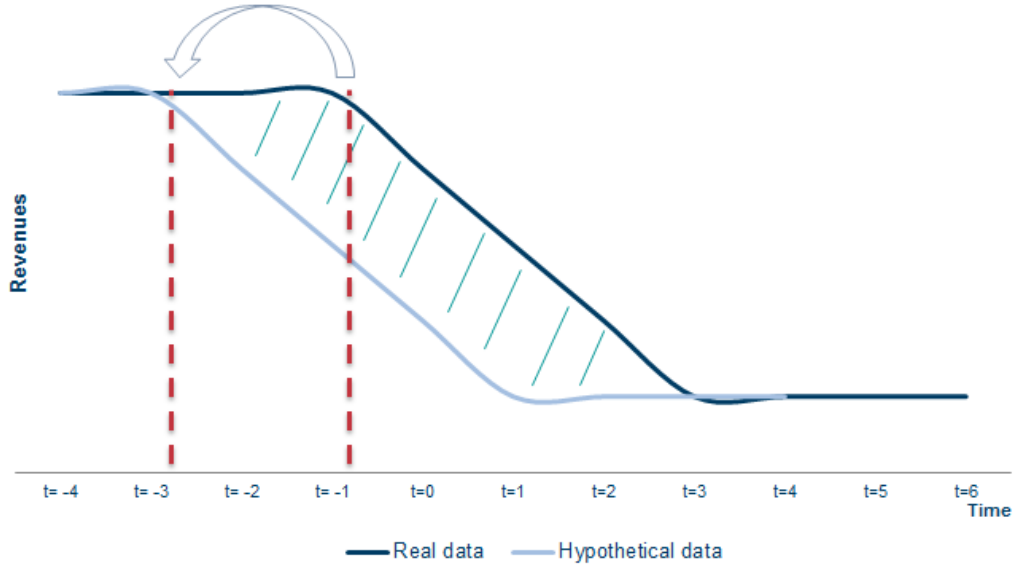
C.8.3 Assumptions

- There is a time lag before the full effect of the 6-month extension disappears. It is assumed that in the hypothetical situation, without SPC extension, the same pattern (relaxation curve) occurs, only 6 months earlier.
- Stabilisation of revenue after the patent expiry is considered complete when the revenues of both situations are approximately equal.

C.9 Methodology to calculate the economic value of Orphan reward

For the orphan products currently on the market, it was not possible to calculate the economic value due to limited availability of real data, stemming from the time of marketing authorisation and time to patent expiry. However, the model presented above and illustrated in the figure below, is following the same reasoning. The only difference is that time is in years and not in quarters.

Figure 42 Model to calculate the economic value of Orphan reward



t=time in years

C.9.1 Assumptions

- Due to the niche market of paediatric orphan drugs, the generic entry will not be as fast as in the 'regular market' (SPC market).
- There is a time lag before the full effect of the 2-year extension disappears. It is assumed that in the hypothetical situation, without the orphan reward, the same pattern (relaxation curve) occurs, only 2 years earlier.
- Stabilisation of revenue after the patent expiry is considered complete when the revenues of both situations are approximately equal.

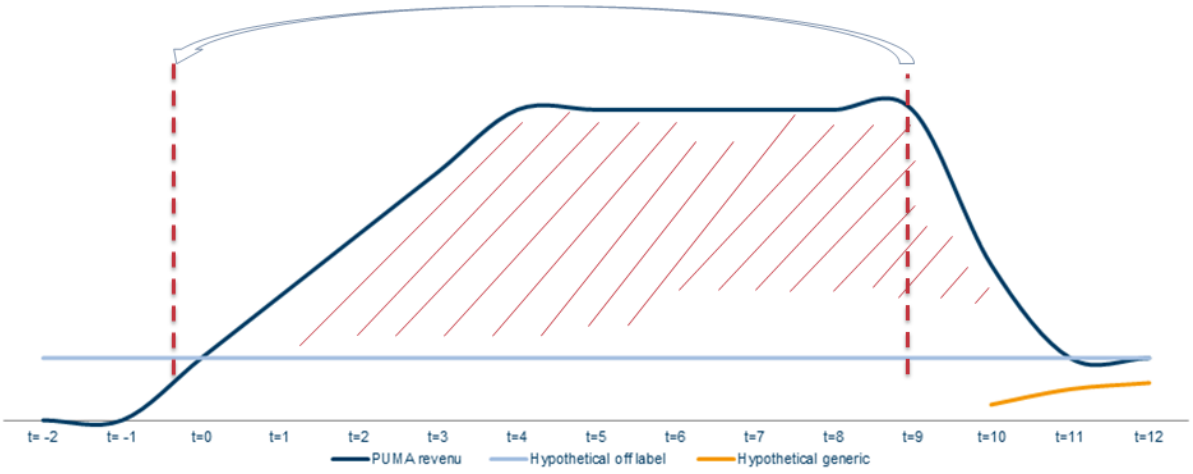
C.10 Methodology to calculate the economic value of PUMA reward

Also for the PUMA products currently on the market, it was not possible to calculate the economic value due to limited availability of real data, stemming from the time of marketing authorisation and time to patent expiry.

For the economic value of the PUMA reward, the difference between the revenues of the last 10 years, before the expiration of the PUMA reward, minus the expected revenues of 10 years without a data/market protection is calculated, see figure below. The revenue of these 10 years without data/market protection (light blue line) is based on revenues of generic products with the same active substance plus a potential premium for prescribing drugs which are also effective in children.

After 10 years of protection, the revenues of the PUMA-holder could still be higher than the revenues of the generic products with the same active substance, due to consumer preferences and delay in generic entry. Therefore, the period over which the economic value should be calculated, may be longer than 10 years.

Figure 43 Model to calculate the economic value of PUMA reward



t=time in years

In this calculation, the redistribution from off-label use to on-label use, by measuring the potential revenue decrease of adult medicines (medicines used by children as off-label drugs), needs to be taken into account. This information (if available) will be identified based on literature review and/or expert opinion.

C.10.1 Assumptions

- Due to the niche market of PUMA drugs, we expect that the generic entry will not be as fast as the 'regular market'.
- There is a time lag before the full effect of the 10-year extension disappears, hence the expression ’10 years (or more)’ is used.
- Stabilisation of revenue after the patent expiry is is considered complete when the revenues of both situations are approximately equal.

Appendix D Socio-economic impact survey

D.1 Profile of survey respondents

Table 41 Survey respondent profile, current position

	Phase I Delphi	**Phase II Delphi**
Researcher at Higher Education Institute/ Public Research Institute/ Charity	41	3
Clinician in Hospital	32	3
Government/ regulatory affairs officer	10	1
Patient representative	8	1
Other (e.g. Researcher at Contract Research Organisation, Research funding programme officer, Clinician in outpatient clinic, Clinical assessor, Family practitioner, Non-profit organisation, Hospital Pharmacist, etc.)	25	2
Total	**116**	**10**

Table 42 Survey respondent profile, paediatric sub-speciality

	Phase I Delphi	**Phase II Delphi**
Oncology	22	2
Neonatology/paediatric intensive care	16	1
Psychiatry	5	1
Gastroenterology/hepatology	4	1
Infectious diseases	4	0
Pneumonology/allergy	4	1
Uro-nephrology	4	0
Cardiovascular diseases	3	1
Endocrinology/metabolic diseases	3	1

	Phase I Delphi	Phase II Delphi
Neurology	2	1
Other (including Immunology/rheumatology, Haematology, Anaesthesiology, Orthopaedic diseases, Pain, Transplantation, multidisciplinary, Paediatric Pharmacology, Palliative care, Paediatric trial management, and unspecified)	49	1
Total	**116**	**10**

D.2 Survey

Appendix E Cost-benefit assessment

E.1 Selected literature review on cost and benefit

E.1.1 A review of the Vernon paper[191]

A "leading article" published in "Pediatric Drugs" in 2012 on "Measuring the patient health, societal and economic benefits of US pediatric therapeutics legislation" estimated the gross economic benefits from the Best Pharmaceuticals for Children Act (BPCA) of 1997 to amount to approximately US$ 360 billion. However, this is not a financial/economic or cash flow benefit, but rather a social or intangible benefit based on some strong assumptions. In particular, it assumes

- an extra US$ 5.9 billion (in 2009 values) of pharmaceutical R&D expenditure generated from 1997 to 2009 (13 years) due to the BPCA[192]
- "1 US life-year produced per US$1,659 invested in pharmaceutical R&D"
- a "life year value" of US$ 100,000

In summary, it is asserted that for the past the benefit/cost ratio to society for such (marginal) investment increase was 100,000/1,659 = 60.3[193]. In other words, for every extra dollar spent society would reap a "benefit" worth more than 60 dollars.

Considering the future, similar high benefits are forecasted: "Depending on the scenario considered, the present value economic benefits of reauthorizing the BPCA range from $136 billion, for a 5-year continuation of the policy with a 6-month market exclusivity extension, to $923 billion, assuming a permanent reauthorization of the market exclusivity extension."[194]

Note that, overall, potential total benefits of more than 1 trillion US$ may be presumed. Earlier in the same paper, in a hypothetical example, for a single medicinal product these estimates are presented: "The pediatric clinical research that identified the (previously unknown) optimal and/or appropriate dosing in children for safe and effective treatment added an additional 107 500 present value life-years, with a dollar value equivalent to between $10.7 billion and $18.7 billion."

It must be noted that *all* of these considerations focus on the single key assumption, that relevant benefits will result from death avoided,[195] and not from cash savings or non-death

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[191] Vernon, J. A., Shortenhaus, S. H., Mayer, M. H., Allen, A. J., & Golec, J. H. (2012). Measuring the patient health, societal and economic benefits of US pediatric therapeutics legislation. Pediatric Drugs, 14(5), 283-294.

[192] Ibid., p. 291-292: This is based on the assumption that of the total R&D expenditure „historically, only 25% of pharmaceutical products have had sufficient clinical data to support a pediatric labelling," that „average R&D productivity can serve as a reasonable approximation of marginal R&D productivity when changes in R&D expenditures are small relative to baseline R&D levels", and that therefore the 6-month extension will trigger 5% more expenditures („As a baseline, we observe that in 1996, the average market exclusivity period for a new molecular entity with market size greater than $100m (2005 $US for the 12-month period prior to generic entry) was 10.04 years."

[193] 60.3 is equal to a (social or societal) return on investment of 5,930% (five thousand nine hundred thirty percent: 6,030 minus 100).

[194] Ibidem, p. 293

[195] Ibid., p. 287: „The mortality assumption is a key structural component of the model."

related intangible benefits. Reflecting on this, one may consider that death is a very rare incidence with children. Of the 32,848 deaths in children between 0 to 14 years old (in the USA in 2013)[196] more than 48% of death occurred around birth and more than 71% of death occurred before the first birthday. The majority of deaths are not related to a specified disease but rather to other causes related to perinatal events and accidents.

According to the study, 23,440 deaths occurred in children under age 1 in the year 2013.[197] Of these, neonatals (under 28 days) account for 15,867 (68%), and postneonatals (28 days–12 months) for 7,573 (32%). For the 1 to 14 year old, 9,408 deaths are recorded. For these, by far the most dominant cause of death was accidents rather than disease-related incidences. The following table presents an extract from a more comprehensive document reporting *inter alia* on the leading causes of death for the USA by age groups (Death rates by age for the 15 leading causes of death in 2013: United States Rates on an annual basis per 100,000 population):

Table 43 Leading causes of death for children, USA, 2013, per 100,000 population

Leading causes of death (ICD 10 codes)	Under 1 year	1–4	5–14	Sum	15–24
Accidents (unintentional injuries) (V01–X59,Y85–Y86)	29.3	8.3	3.7	**41.3**	26.4
Diseases of heart (I00–I09,I11,I13,I20–I51)	7.8	1.1	0.4	**9.3**	2.1
Malignant neoplasms (C00–C97)	1.6	2.1	2.2	**5.9**	3.4
Influenza and pneumonia (J09–J18)	4.5	0.6	0.3	**5.4**	0.4
Septicemia (A40–A41	3.9	0.3	0.1	**4.3**	0.3
Cerebrovascular diseases (I60–I69)	2.7	0.2	0.2	**3.1**	0.3
Chronic lower respiratory disease (J40–J47)	0.6	0.4	0.4	**1.4**	0.4

Source: Jiaquan Xu, M.D. et al, op. cit. Own excerpt from "Death rates by age for the 15 leading causes of death in 2013: United States Rates on an annual basis per 100,000 population"

The data in table Table 43 show that accidents are by far the most prevalent cause of death for children aged 0-14. As a cause, they occur 4.4 times more than diseases of the heart, 7 times more than cancer, and 7.6 times more than influenza and pneumonia, the most important diseases accounting for the death of children. For the 14-24 years age group, the rates are even higher (i.e. 7.8 to 88). At the same time, this table identifies those disease areas

[196] In the absence of similarly detailed data and to compare with the paper mentioned, we make use of USA data here.

[197] For all data, see Jiaquan Xu, M.D.; Sherry L. Murphy, B.S.; Kenneth D. Kochanek, M.A.; and Brigham A. Bastian, B.S (2016). Deaths: Final Data for 2013. National Vital Statistics Reports, Volume 64, Number 2 February 16, 2016. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System.

where pharmaceutical/clinical research may have the highest impact on the avoidance of death in children.

In this context, also the data reported by WHO respectively in the Rand study[198] on "Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use - Prepared for the European Commission" indicate that death due to adverse drug reactions (ADRs) is relatively uncommon in young people:

Table 44 Adverse drug effects as a cause of death in the EU-15, 1999 (deaths per million population)

	Entire population	**0-24 year olds**
Austria	0.12	0.00
Belgium	3.05	0.00
Denmark	0.19	0.00
Finland	0.00	0.00
France	11.07	0.32
Germany	6.27	0.50
Greece	0.00	0.00
Ireland	1.34	0.00
Italy	0.33	0.13
Luxembourg	18.48	0.00
Netherlands	2.72	0.62
Portugal	1.30	0.31
Spain	3.94	0.49
Sweden	8.13	0.00
United Kingdom	0.77	0.11

Source: WHO Mortality Database

[198] Oortwijn et al. Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use. Prepared for the European Commission. Rand Europe, 2004, p. 33

The deaths of children of age 0-15[199], according to the US death data register amounts to 32,848 deaths for 2013, of which 3,993 were caused by accidents, and 15,867 to perinatal events. In total, 12,988 deaths are related to diseases, where medicines could play a considerable role in treatment. The Vernon paper may have overstated some of the ADEs in children. Another paper finds that "Each year, approximately 26 500 American children (to age 18 years) die from ADRs."[200]

A more reasonable plausibility calculation on this issue may be as follows:

In 2013, the overall death was 2,596,993 for the US. Deducting from this perinatal deaths of children (15,867) and overall deaths by accident (130,557) leaves 2,450,569 deaths mostly from diseases. The US Institute of Medicine landmark study on "To err is human"[201] estimates that at least 44,000 and as many as 98,000 people die in any given year from medical errors[202] that occur in hospitals. From all adverse events that led to death, *over half* "resulted from medical errors and could have been prevented."[203] [204]This implies that almost another half of all deaths resulted from other ADEs which may be caused by medicines. Assuming this number is the mean of 44,000 and 98,000 we calculate with 71,000 deaths. On the base of 2,450,569 deaths for all, this leads to a death rate of 0.029 or 2.9%. Applying this to the about 13,000 deaths of children <15 years old related to diseases, we obtain a figure of 377 deaths which may be due to ADEs. How many of these events are indeed due to ADRs, i.e. where there exists a causal relationship to the drug(s) administered, is unknown. Assuming this ratio to be 50%, we arrive at a death figure of about 190. Next, noting that off-label use of paediatric medicines may be anywhere between 25% and 50%, taking the mean value of this as 37.5 and assuming that off-label use is causing somewhat more ADRs causing death, one can estimate that perhaps 40% to 50% of death may be related to off-label use, or as a mean value of 45%, out of 190 around 85 deaths per year.

How many of these deaths could be avoided by switching from off-label to on-label use is an unknown variable; we would expect it to be anywhere between 10% and 25% or, for a value of 20%, 17 deaths overall, in relation to the US population (and, keeping everything else constant, approximately 27 deaths in relation to the EU population).

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[199] Jiaquan Xu, M.D. et al, op. cit. The next age bracket, for which data are reported, is 15 to 24. See

[200] Carleton, B. C., & Smith, M. A. (2006). Drug safety: Side effects and mistakes or adverse reactions and deadly errors? British Columbia Medical Journal, 48(7), with reference to Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA (1998) 279:1200-1205.

[201] Kohn, L. T., Corrigan, J. M., & Donaldson, M. S. (Eds.). (2000). To err is human: building a safer health system (Vol. 6). National Academies Press.

[202] Examples given are overdose during chemotherapy, the wrong leg amputated, death during "minor" surgery due to a drug mix-up. Ibid., p. 1

[203] Ibid., p. 1

[204] Studies performed in Europe indicate that the situation is similar across healthcare systems. A recent update on the USA led to the result that since 2000 not significant change has happened.

E.1.2 Economic return to industry of clinical trials performed under the US paediatric exclusivity programme[205]

In 1997, the US Congress authorised the Food and Drug Administration (FDA) to grant 6-month extensions of marketing rights through the Pediatric Exclusivity program if industry sponsors complete FDA-requested paediatric trials. On the one hand, the program has been praised for creating incentives for studies in children. On the other hand, it has been criticised as a "windfall" to the innovator drug industry. The paper reports on analysing this issue for the period 2002 – 2004. Data from 59 therapeutic agents were submitted to the FDA. The authors obtained the final study reports from 9 drugs in a broad range of therapeutic areas, guided by a specific selection algorithm. It turned out that "the distribution of net economic return for 6 months of exclusivity varied substantially among products." The "net return ranged from (−)$8.9 million to (+)$507.9 million." The ratio of return to cost ranged from −0.68 for one product to between 2.31 (131%) and 73.6 (7,260%) for the remaining ones.

E.1.3 Assessment by the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

The assessment undertaken by the German Federal Institute for Medicinal Products is of a more qualitative nature, attempting to trace certain developments since implementation of the EC Paediatric Regulation 1901/2006 and its practical relevance for treatment in Germany.[206] Based on data obtained from EMA and the "Heads of Medicines Agencies (HMA)"[207] they report that until December 2011 1,144 PIPS were submitted to EMA. 74% were for new, not yet authorised medicines, 24% pursuant to Art. 8 for products still under protection, and 2% for patent-free products pursuant to Art. 30. By Feb. 2014 the numbers had increased to 1,556 applications, 329 waivers, 715 accepted PIPs, and 54 finished ones, without significant shifts in their respective proportions.

These data are then contrasted with the prescription behaviour of German physicians when treating young people 0-17 years old. For the five most relevant indications, the 20 most prescribed active ingredients (ATC codes) in 2011 were identified for each field, and for two groups of patients – those 0-11 and 12-17 years old. Due to overlap, overall 124 active ingredients were included into further analysis. Data concern only the ambulatory sector. One objective was to explore whether the medicines were on-label for children. Overall, around 90% of all prescriptions focused on the top 20 active ingredients in each field:

- Pulmonary/ENT diseases: 18m prescriptions (85% on the top 20 ingredients)
- Infectious diseases: 7.4m (97%)
- Central nervous system incl. pain: 5.6m (94%)
- Cardiological/heart diseases: 235,000 (75%)

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[205] Li, J. S., Eisenstein, E. L., Grabowski, H. G., Reid, E. D., Mangum, B., Schulman, K. A., ... & Benjamin, D. K. (2007). Economic return of clinical trials performed under the pediatric exclusivity program. Jama, 297(5), 480-488.

[206] All data and information in the following section relate to Afentaki, A. (2014). Arzneimittel für Kinder und „Off-Label-Use "5 Jahre nach Inkrafttreten der EU-Verordnung (EG) Nr. 1901/2006. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 57(9), 1111-1119

[207] „The Heads of Medicines Agencies (HMA) is a network of the heads of the National Competent Authorities (NCA) whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area." http://www.hma.eu/abouthma.html

- Oncology 29,000 (91%)

Around 77% of all active ingredients were identified as "on-label" use for children, 18.5% as "off-label", and 5% as "undefined". The highest rate – 37% - of off-label use was in oncology for children up to 11 years old, whereas for infectious disease-related prescriptions no off-label use was identified.

In our context, it is relevant that for the 124 most often prescribed active ingredients *only one* was still under patent protection because the others were authorised long before 2007. Nevertheless, for 16% of these ingredients a PIP had been accepted, noting that 74% of all submitted PIPs relate to new ingredients, which therefore cannot yet be prescribed.

In summary, the assessment concludes that so far only very few studies have been finalised, whereas most are still in the planning or implementation stage, particularly those concerned with new active ingredients. The Paediatric Regulation was a first, most important step ("milestone") to improve the on-label prescribing of medicines for children, but so far, only a modest start was achieved. As most results from PIPs and other measures are still to come, "however only the children and adolescents of tomorrow" will fully profit.[208]

E.1.4 Review of the Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use

It us useful to revisit the impact predictions made by the Rand study on "Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use," undertaken for the European Commission in 2003/4.[209] *Inter alia*, it pointed out that

- "The Regulation will cost money", and "consumers will have to pay higher average prices for medicines for paediatric and adult use."
- "Better testing, safer medicines, and the greater availability of tested medicines will improve health care for children and reduce the prevalence of ADRs and the burden of childhood disease." … "Although the extent of the reduction in costs cannot easily be determined, it will most likely more than compensate for the increase in average drug prices brought about by the delay in the marketing of generic alternatives."
- "The main social impact will be that the increased availability of medicines tested for use in children – without a substantial rise in medicinal prices – *will provide the opportunity*[210] to avoid preventable ADRs, raise the quality of medicinal treatment for children, and thus improve their quality of life. The proposed Regulation will therefore achieve its highest objective."

Perhaps most interesting, particularly in view of the results from the German study, is the final assessment: "The higher objective of the Regulation –the very reason why it was drafted in the first place– is to improve the health of the children of Europe. *The proposed Regulation provides one half of the solution*. By changing the economics and legal preconditions of the production of medicines, the Commission hopes to steer consumers

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[208] Ibid., p. 1118

[209] Oortwijn et al., op. cit., pp. 81-86

[210] Italics by the study team

(health care professionals and households) towards tested and, hence, safer and more effective medicines. *If the tested medicines are indeed prescribed,* children will receive better treatment, involving shorter hospitalisation and lower drug consumption, and enjoy a higher quality of life. A number of risks and uncertainties remain, but the most likely ones do not substantially threaten the impact of the Regulation. Choice remains the most uncertain factor: the readiness of the industry to focus on the development of paediatric medicines, the response of generic drug manufacturers to the incentives of the PUMA, and the willingness of health care professionals to prescribe tested medicines. *The final piece –regulating prescription practices– will have to be provided by policy makers in the health care domain.*"[211]

In other words, planning and executing PIPs and other measures, improving labelling and generating more knowledge on treatment of children are only "one half of the solution". As long as the second half of the solution is not assured, as long as the new knowledge is not translated into clinical practice and widely applied for better healthcare for children, the overall impact will remain small. Knowledge as such may have considerable intellectual, intangible value in satisfying our curiosity, but as long as it is not diffused and applied in paediatric healthcare provision, it does not generate economic or social value.

E.2 Defining and identifying adverse drug reactions and events

E.2.1 Adverse drug reactions (ADRs)

Following widespread discussions in the literature[212], the key benefits to be considered derive from major and minor adverse drug reactions (ADRs) avoided due to the improved information on how to better apply the medicinal product under analysis to children (switch from off-label to on-label use, identification of new paediatric indications, etc) and the improved therapeutic outcomes there from.

The WHO defines ADRs as: "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function." [213]ADRs are injuries caused by taking a medication. They are appreciably harmful or unpleasant reactions, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure)."[214]

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[211] Italics by the study team

[212] Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, et al. (2012) Adverse drug reactions in children–a systematic review. PLoS One 7: e24061.

[213] http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

[214] Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. The Lancet, 356(9237), 1255-1259.

E.2.2 Adverse drug events (ADEs)

ADEs *injuries occurring at the time a drug is used*, whether or not it is identified as a cause of the injury. The American Food and Drug Administration (FDA) defines ADEs as "any *undesirable experience associated* with the use of a medical product in a patient."

EMA defines an Adverse Event as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product[215]."

Concerning the severity of such ADEs, it has been proposed to classify them as[216]:

- Significant
- serious, and
- life threatening

It follows that ADRs are a subset of ADEs.

According to FDA, a "serious adverse event" is one when the patient outcome is one of the following:[217]

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Other Serious (Important Medical Events)

The rare disability impact seems to be mostly of a temporary nature[218], but some can be life-long.

E.2.3 Medication errors (MEs) and ADEs

A related concept is that of medication error. It has been defined as "any incorrect or wrongful administration of a medication, such as a mistake in dosage or route of administration, failure to prescribe or administer the correct drug or formulation for a particular disease or condition, use of outdated drugs, failure to observe the correct time for administration of the drug, or lack of awareness of adverse effects of certain drug combinations."[219] Typical errors relate to "underdose, overdose, wrong drug choice, error in

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[215] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

[216] Holdsworth, M. T., Fichtl, R. E., Behta, M., Raisch, D. W., Mendez-Rico, E., Adams, A., ... & Greenwald, B. M. (2003). Incidence and impact of adverse drug events in pediatric inpatients. Archives of pediatrics & adolescent medicine, 157(1), 60-65.

[217] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm

[218] Holdsworth, M. T , Ibid.

[219] http://medical-dictionary.thefreedictionary.com/medication+error

frequency, error in timing, excessive infusion rate, lack of premedication, wrong route, drug interaction, and dispensing error."[220] It follows that medication errors may lead to an ADE or even an ADR, but they do not always have an adverse clinical consequence.[221] "Several studies suggest that about one third of ADEs are associated with medication errors and are thus preventable."[222] This implies that ADEs and MEs are distinct sets, but have an overlapping subset.

E.2.4 Validity and reliability of data reported in studies – a summary

In their study on "How are medication errors defined?" Lisby et al. note: "In the Harvard Medical Practice studies of adverse events in hospitals, medication errors were found to be the main contributor constituting around one in five of the events, which were subsequently confirmed in comparable studies and studies of adverse drug events (ADEs)." The documented prevalence of medication errors "ranged from 2% to 75% with no associations found between definitions and prevalence… It appears that definitions and methods of detection rather than being reproducible and reliable methods are subject to the individual researcher's preferences."[223] They also found that a certain set of studies from institutions in Boston reported consistently low "occurrence of medication errors ranging from 2% to 8% regardless of whether intercepted errors were included or not, suggesting consistency in error detection methods. However, prevalence in the two studies from Europe exceeded the American studies by as much as eight times, despite use of virtually identical definitions. No obvious circumstances can explain these extreme differences, apart from use of data collection methods."[224]

In summary, the widely differing conceptual definitions of the terms used, their operationalisation, and in particular their empirical measurement in a specific context explain the absence of overriding consistent, comparable and reliable data on ADRs, ADEs and MEs prevalence. The context of such studies usually relates only to a certain setting like a single or a group of hospitals at the secondary or tertiary level, the ambulatory setting of emergency rooms, community centres etc. in a certain town or region, often also concerning only a given disease – all of this leading to the widely divergent results as e.g. summarised in the study on "Adverse drug reactions in children."[225]

E.2.5 Objective of the modelling approach and reporting of adverse drug events by medicine agencies

The focus of this study is on estimating the potential socioeconomic impact of the Paediatric Regulation, specifically in relation to new knowledge generated by successful and

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[220] Holdsworth, M. T , Ibid.

[221] Carleton, B. C., & Smith, M. A. (2006). Drug safety: Side effects and mistakes or adverse reactions and deadly errors?. British Columbia Medical Journal, 48(7), 329.

[222] Kaushal, R., Bates, D. W., Landrigan, C., McKenna, K. J., Clapp, M. D., Federico, F., & Goldmann, D. A. (2001). Medication errors and adverse drug events in pediatric inpatients. Jama, 285(16), 2114-2120.

[223] Lisby, M., Nielsen, L. P., Brock, B., & Mainz, J. (2010). How are medication errors defined? A systematic literature review of definitions and characteristics. International Journal for Quality in Health Care, 22(6), 507-518.

[224] Ibidem, p. 516

[225] Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, et al. (2012) Adverse drug reactions in children–a systematic review. PLoS One 7: e24061.

unsuccessful PIPs. The PIP investigations contribute to improving "the information available on the use of medicinal products in the various paediatric populations."[226] In other words, the major objective of a PIP is to generate new knowledge so that a given medicinal product may be used on-label rather than off-label or not at all when treating a child and can help prevent ADEs. Also, a recommendation to not use the medicine for this population may be the outcome of a successful PIP.

The benefits resulting when applying this new knowledge are to be contrasted with "the maximum cost [which] will concern the added 'monopoly rent' resulting from a six-month patent extension" to the healthcare system respectively the payers.[227]

Given the above-discussed situation on reliably measuring ADEs, we use the EMA and FDA data from their pharmacovigilance resources for our purposes.

E.2.6 European Medicines Agency (EMA)

The EMA is responsible for the development, maintenance and co-ordination of EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance), "a system for reporting suspected cases of adverse reactions to a medicine" within the European Economic Area (EEA) and globally. It collects for authorised medicinal products, amongst others, "individual case safety reports (ICSRs): A document providing information related to an individual case of a suspected side effect due to a medicine." Information is collected on both "serious" and "non-serious" suspected adverse reactions. The purpose is the "early detection and evaluation of possible safety signals: Information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature."[228] These quotes contain the terms suspected adverse reaction, suspected side effect, and adverse event. Therefore ISCRs are limited to events in which causality is suspected, and hence not every adverse event should be reported. We assume for our purposes that the term *adverse drug event* probably best characterises the information collected.[229]

It also includes information on medication errors: "Pharmacovigilance legislation requires reporting of medication errors that result in adverse reactions to EudraVigilance." And Directive 2010/84 (EC) in its recital (5) stipulates: "For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at

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[226] Recital (4) of the Regulation; cf. also Art. 2 2.: „'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population"

[227] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm, p. 9

[228] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac05800241de

[229] Blake, K.V. Et al. (2014) in their paper "Comparison between paediatric and adult suspected adverse drug reactions reported to the European medicines agency: implications for pharmacovigilance" (Pediatric Drugs, 16(4), 309-319) do not even discuss this issue and just assume that they are writing about ADRs.

normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product."[230]

E.2.7 US Federal Drug Administration (FDA)

In the USA the information is more clearly defined, FDA consistently talks only about "adverse event and medication error" reporting: Its "Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products."[231]

E.2.8 Making use of ADE data from regulatory agencies

As EMA and FDA seem to primarily collect information and data on ADEs, this is the concept which will be applied in what follows, and we will make use of their data as far as possible as input to our benefit-cost model.

For what follows, it is to be observed that, e.g., ADEs resulting from medication errors cannot be prevented through data obtained from executing PIPs. Rather, these types of challenges need investment in better understanding of unexpected events and medication management processes. "Two paradigms have been suggested to explain precursors to medication errors and develop interventions to prevent them: accident theory and high-reliability organizational theory."[232]

As ADEs are defined as any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury, the number of ADEs registered is probably considerably larger than the number of correctly identified ADRs for the same medicine. The later requires an active analysis of a cause-effect relationship, which may be difficult to establish. This can be illustrated by the following examples:

In a "Pediatric Focused Safety Review: Diovan®"[233] at an FDA Pediatric Advisory Committee Meeting (June 23, 2009)[234] on, amongst others, pediatric exclusivity studies, information on two ADE reports concerning deaths were observed, but in both cases these were not ADRs. The drug is an angiotensin II receptor blocker (ARB) and administered to treat high blood pressure. The "Safety Assessment" of the two deaths was as follows:

- "(South Africa) 1 year old female with HTN, complex congenital urologic anatomy, recurrent UTI, on multiple medications
  - Died during OL [open label] phase after developing severe vomiting and diarrhea
  - Death ascribed to gastroenteritis

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[230] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/03/WC500139871.pdf

[231] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/

[232] Carleton, op. cit.

[233] A product included in the later detailed analysis.

[234] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM168549.pdf

- (India) 1 year old male with multiple congenital anomalies and comorbidities, including single kidney, HTN and on multiple medications
  - *Died from pneumonitis* 11 days after discontinuation from OL [open label] study participation due to hepatitis."

In the same report, for the USA for the period 1996 to 2008 three deaths of children <17 years old are reported due to "transplacental exposure", i.e. death of unborn babies, a situation not susceptible to a PIP study. FDA excluded them from their final tabulation of ADEs.

In an FDA clinical paediatric review of Anastrazole[235] (also covered later by detailed assessment) these statements on ADEs reported should be noted: "Three patients (10.7%) experienced four serious adverse events [SAEs]... Two patients experienced femoral fractures (one patient had two such events) and one had a right ovarian cyst. *None of these SAEs was judged related to the study treatment*." And: "A total of 24 (85.7%) patients experienced at least one adverse event. Adverse events that occurred with a frequency >10% (i.e. in ≥3 patients) were upper respiratory tract infection (21.4%), cough (17.9%), pharyngitis (14.3%), pyrexia (14.3%), arthralgia (10.7%), ear infection (10.7%), gastroenteritis (10.7%) and nasopharyngitis (10.7%). With the possible exception of arthralgia, *all the above-listed AEs represent commonly encountered childhood illnesses and symptoms*."[236]

For the purpose of this study, data on ADRs would be the correct reference base. Clinical trials on a specific drug can help to improve labelling information to avoid ADRs, but they will not allow to prospectively avoid ADEs not related to labelling advice. However, as no (reliable) sources with representative data of ADRs related to the medicinal products under investigation are available, we have to make do with ADE reports. This implies that in all likelihood the data on ADEs used overestimate the potential impact a PIP may have on future ADRs.

E.3 The basic elements of the modelling approach

This section presents the modelling approach and its basic structure. The various variables and their interpretation are discussed, followed by a summary table of the initial results achieved.

An initial structuring of cost and benefit indicators allows conceptualizing in detail the features of the cost-benefit analysis model. Such structuring as depicted below also exhibits the data needs of the cost benefit analysis (CBA). The CBA model builds on the analysis presented in previous chapters. The indicator development and model conceptualisation help validating (i) availability of relevant data and access, and (ii) filling information and knowledge gaps relevant for the exploratory CBA.

The CBA model of the economic impact of the Paediatric Regulation was developed foremost as a conceptual tool, which can be used flexibly dependent on data availability, stakeholder

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[235] CLINICAL REVIEW of Anastrozole by Dragos Roman. FDA, September 5, 2007, p. 8; available at http://www.fda.gov/downloads/Drugs/DevelopmentApproval Process/DevelopmentResources/ucm129540.pdf

[236] Ibid., p. 55

perspective, and policy need. The model is populated with realistic data (1) to generate meaningful results regarding overall impact on healthcare systems, and (2) to test if the model is sufficiently robust.

In the following sections, we discuss the indicators and data relevant to costs and benefits of the Regulation. Paediatric Regulation foresees a six-month extension of the supplementary protection certificate (SPC)[237] after completion of a paediatric investigation plan (PIP)[238] and upon receiving positive statement of compliance. In line with this extension period, initially our reference for calculating costs and benefits will also be for a six-month time span, and calculate (or estimate) all the variables required as input for populating the Cost-Benefit Model. Of course, the period for which benefits may accumulate can be extended to for a longer, e.g. 10 years in order to gross-up the results.

In the current study, we aim to evaluate the economic aspect of the Paediatric Regulation and, in addition, effort was also made to include, to a lesser extent, aspects of social/societal benefits.

E.3.1 Measuring the prevalence of adverse drug events in Europe

Research indicates that, depending on the country and the period, between 23% and 50% of the medicines prescribed for children were not tested for use in the specific age group (off-label use) and that only a limited number of medicinal products was developed specifically with children in mind. This absence of specifically tested products often leaves doctors with no alternative but to use products 'off-label' with the associated higher risks of inefficacy or adverse reactions.[239]

The incidence of an ADE relates to a specific child undergoing a therapeutic intervention with the medicine in question. For this study, it is termed a treatment episode. Consequently, in order to approach the issue of ADEs, a first step in our overall calculations to populate the Cost-Benefit Model is to arrive at a rough estimate of the number of paediatric treatments resulting from the use of the medicinal product under investigation during the 6 month extra SPC period. The starting point is the overall wholesale revenue obtained by the marketing authorisation holder (industry) for the medicinal product as identified in relation to the 6 months SPC extension, plus quantity information on the drugs involved (like number of tablets to which the revenue relates).[240]

Depending on the medicinal drug, the average duration of a treatment episode can vary greatly. For example, a medicinal product, which is prescribed for a chronic disease, needs to be taken by the patient during a prolonged period, maybe even during its remaining lifetime.

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[237] http://ec.europa.eu/health/sites/health/files/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf, Annex II

[238] Ibidem, p. L 378/2. A PIP "is the document upon which the development and authorisation of medicinal products for the paediatric population should be based. The paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. Since the paediatric population is in fact composed of a number of population subsets, the paediatric investigation plan should specify which population subsets need to be studied, by what means and by when." And in Art. 2. 2): "'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population"

[239] SANTE/2015/D5/023, p. 1

[240] These calculations are based on wholesale list prices. In reality, depending on the context, the price paid may vary, probably it is somewhat lower. On the other hand, it is known that not all paid for and dispensed medications are indeed taken by patients.

The treatment of infectious diseases like influenza, on the other hand, last on average between five and ten days usually. Therefore, the average duration is an important variable in the CBA model. Based on the typical dosage information found in the patient information leaflet and in combination with information about the typical duration of the treatment, the average number of a medicine's units (tablets, drops, puffs…) per episode was derived. This information was then discussed with an experienced pharmacist and corroborated or adjusted. Dividing the quantity information by the number of units per episode, the total number of treatment episodes was calculated.

For example, Drug B is used to treat migraine headache. If the first pill does not help, the patient should be given another one at least two hours later, but not more than three in 24 hours. For children, however, a maximum dose of 1 pill per day is proposed. Therefore, we assume that on average one migraine episode requires only 1.5 pills, based on the observation that it seems that often the package size is 2 pills, and that some children will take 2 pills over 2 days.

For estimating the share of treatment episodes relating to paediatrics only, the cases of reported ADRs in the EudraVigilance database are taken. Data is provided there by national medicines agencies, physicians, patients and others more or less in relation to the actual distribution of therapeutic interventions – the intake of the prescribed medicine – across the whole population. The number of ADE reports for babies and children up to the age of 17 (due to fixed categorisation in the database) are represented as share of all reports – the figure used in our calculations. Because not all reports provide age information, this figure is a lower estimate, because all reports with no age reference are counted by us as reports for adults. These data were, as far as possible, checked against and corroborated by FDA data. An example may illustrate this:

- In its "Pediatric Focused Safety Review" of Singulair (active ingredient: montelukast sodium) the USA FDA reported these figures on prescriptions for montelukast by patient age.[241] About 38% of all patients were below the age of 17.

When checking against the ADE reports data as published by EMA,[242] we obtain very similar percentage data concerning "the number of individual cases identified in EudraVigilance for Montelukast": it is "7,606 (up to June 2016)". The reported numbers of individual cases by age group are presented in the table below.

Table 45 ADE reports by age group

Age Group	Cases	%
Not specified	1,349	17.7%

[241] Kalra, D. Gatti J. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review: Singulair (montelukast). 2 September 2014. Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM414065.pdf

[242] https://bi.ema.europa.eu/analyticsSOAP/saw.dll?PortalPages. http://www.adrreports.eu/en/search.html

Age Group	Cases	%
0-1 month	51	0.7%
2 months – 2 years	416	5.5%
3-11 years	1,789	23.5%
12-17 years	585	7.7%
18-64 years	2,579	33.9%
65-85 years	776	10.2%
More than 85 years	61	0.8%
Total	**7,606**	**100.0%**

This yields 37.4% of all reports which can be definitely allocated to below 18-year-old patients. From this we deduce that similarly in Europe about 38% of all treatment episodes relate to patients below the age of 18 years. The handling of these variables in our model is summarised in the table below.

Table 46 Summary of ADE related variables used in the CBA model

Indicator name	Number of paediatric treatments resulting from the use of a medicinal product during the 6-month SPC extension
Variables	Medicinal product revenues during 6 months SPC extension (€) Average amount of units of the medicinal product per episode (tablets, drops, puffs…) Average price per one unit of the medicinal product (€) Share of treatments with the medicinal product relating to paediatrics only (%)
Formulae	Revenues / (Dosage per episode * Average price per unit dose) * Share relating to paediatrics
Example	Drug A is used to treat chronic respiratory diseases such as asthma. The average dosage per episode is one tablet daily, every day. For the six-month observation period in this assessment, this amounts to approx. 182 pills. With the average market price of the product and the product revenues for the six-month period known (data available for eight EU countries), the total number of episodes is calculated to be 430,000. With about 38% of all reported ADR cases occurring in the population under 17, the share of treatments relating to paediatrics is estimated to be approx. 161,800 treatment episodes.

In a further step, we arrive at an estimate of how many ADEs may have resulted from these episodes. Usually, no detailed data on this are available from European sources. However,

FDA indirectly reports such data, eg as can be illustrated for Singulair (active ingredient: montelukast sodium).

As noted above, during the period March 26, 2012- September 26, 2013 FDA registered 8,798,502 patients "receiving dispensed prescriptions for Montelukast".[243] [244] During the same period, 1,148 reports on adverse events were received for adults (17 years and older), and 731 for children:

Note that the US/FDA data use as a comparator the "Nationally Estimated Number of Patients that Received A Dispensed (…) Prescription From U. S. Outpatient Retail Pharmacies, Stratified by Age." (Source: IMS Vector One®: Total Patient Tracker (TPT))[245] This implies that independent of the number of treatment episodes an individual patient is counted only once.[246] Compared to our 'treatment episode' approach, using such data will lead to some overestimation of the prevalence of ADEs because a single patient may encounter some to even many such episodes. This implies an overestimation of the actual number of ADEs when applying a treatment episode approach.

A detailed analysis then led to the following results for children with respect to the reliability of these reports, as presented in Figure 44. In summary, for the overall 3,307,328 dispensations for patients below the age of 17, overall 548 "serious pediatric cases" were reported, of which 140 concern "serious pediatric reports (including death, life-threatening, hospitalization or disability)", including "4 deaths".[247]

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[243] Erica D. Radden. Pediatric Focused Safety Review: Singulair (montelukast sodium). Pediatric Advisory Committee Meeting September 23, 2014, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM417346.pdf

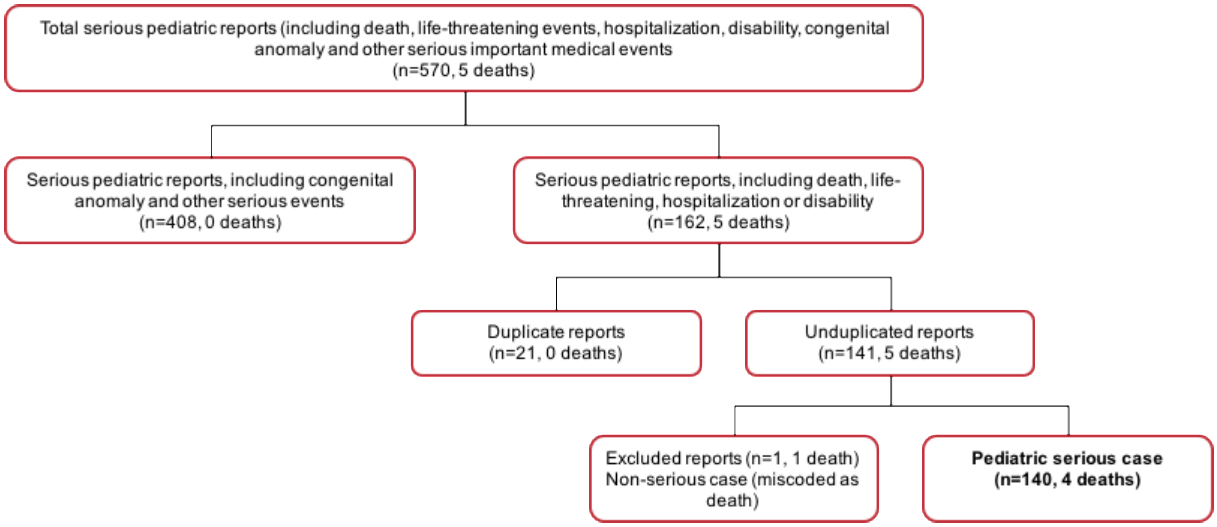
[244] This does not imply that all prescribed and dispensed medicines were indeed taken. It is known that up to 40% and more of prescribed medicines are not picked up, and that of the dispensed ones 25% and more are not taken by patients after reading the drug information provided. The scientific institute of the large German statutory health insurance AOK, in its report „Zu Risiken und Nebenwirkungen: Lesen Sie die Packungsbeilage?" (by Nink, Katrin / Schröder, Helmut (2005). Wissenschaftliches Institut der AOK -WIdO (ed.), WIdO-Materialien Bd. 53, Bonn) estimated this value, based on representative interviews with patients, at around 28% (p. 56). See also Sarah Almanie (2015). ECONOMIC IMPACT OF WASTE IN PRESCRIBING, DISPENSING, AND MEDICATION CONSUMPTION IN THE UNITED STATES. Virginia Commonwealth University thesis, VCU Scholars Compass: "The rate of abandoned prescriptions also had a wide range in the literature (from 3.27% to 28.3%)."

[245] Donna L. Snyder. Slides for "Pediatric Focused Safety Review: … Drug B benzoate." Pediatric Advisory Committee Meeting, April 21, 2014, FDA

[246] Note however: "Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts." Ibidem.

[247] When neither FDA review or other reports nor a detailed web search delivered any indication of death from ADEs (or ADRs), we assumed that such events were absent.

Figure 44 FDA case selection of serious paediatric cases



Source: based on Donna L. Snyder. Slides for "Pediatric Focused Safety Review: ... Rizatriptan benzoate." Pediatric Advisory Committee Meeting, April 21, 2014, FDA

Overall, this yields an estimated 0.0166% ADRs per episode. Translating this to the 161,800 episodes calculated for EU countries for the 6 month SPC period, we obtain a rough estimate of 27 ADRs for the EU countries included in the analysis.

In cases where no FDA data were available, a complementary approach based on the EudraVigilance data base reports[248] was performed. To illustrate this again for Drug A, we take the total number of ADE reports for children below the age of 18 in EudraVigilance, which is 2,844. Then, based on the assumption that this figure covers at least 10 years[249], we set it into relation to the 6 month period under consideration (i.e. we divide it by 20); this renders us a value of 142. Next, noting that only 23.5 % of all reports in EudraVigilance relate to the European Economic Area (EEA), we multiply it by this figure, which gives us 33.4 ADEs. Comparing this with the 34.3 ADEs calculated for our period and for Europe based on the FDA data leads to an almost identical result. Although this is not a proof that this approach is the most appropriate, we compared the results also against other medicinal products and find a surprisingly close approximation. Furthermore, the surprising conformity between FDA and EMA data should suggest that across the developed countries

[248] On the quality of these data, EMA on ist website http://www.adrreports.eu/en/data_quality.html reports as follows: „Data quality - The European Medicines Agency is responsible for hosting and maintaining EudraVigilance, a system designed for collecting reports of suspected side effects, used for evaluating the benefits and risks of medicines during their development and monitoring their safety following their authorisation in the European Economic Area (EEA). - The data displayed on this website through the web reports are submitted electronically to EudraVigilance by national medicines regulatory authorities and by marketing-authorisation holders (pharmaceutical companies). As a result, the Agency has limited control over the completeness or accuracy of the information available.

The Agency does carry out quality reviews in EudraVigilance, which includes identifying duplicate reports, performing the coding of the reported medicines and reported active substances, and providing feedback on the quality of information sent by national medicines regulatory agencies and marketing-authorisation holders.

[249] In reality, they will usually cover several more years as they report over the whole life cycle of a medicine, but such data is not available.

reporting of ADEs is relatively reliable and consistent. The handling of this variable and calculation in our model is summarised in Table 47.

Table 47 Summary of ADR variables used in the CBA model

Indicator name	Number of paediatric ADRs per 6 month SPC extension
Variables	Number of paediatric episodes Number of paediatric ADRs as % of episodes Number of paediatric ADRs Number of reported serious ADR cases
Formulae	Number of serious paediatric cases/dispensations for paediatric population * number of paediatric episodes
Example	For Drug B, from 3,307,328 dispensations for patients below the age of 17, overall 548 serious paediatric cases were reported, This amounts to 0.0166% ADRs per episode. Divided by the 161,800 episodes calculated for the 6 month SPC period, the result is 27 ADRs for the EU countries included in the analysis.

E.3.2 Benefits from avoided mortalities

Wherever any information on very serious ADRs resulting in death was available, the respective figures were used for our calculations. To refer to the earlier example of Montelukast, FDA reported a total of 4 paediatric serious case reports concerning death as resulting from the 3,307,328 dispensations for patients below the age of 17. Relating this to all serious ADRs of 548, this implies that here 0.73% of all validated reports concern a death of a child; relating this to the 3,307,328 dispensations for patients below the age of 17, the death ratio is 0.00012%. For our European values, this implies a hypothetical absolute number of deaths of 0.196.

As no empirical data are available on the impact of a PIP on the reduction of ADRs, we assume in all instances that the value is a reduction by 20%. This seems to be a relatively high value which is based on the perhaps quite optimistic assessment found in the literature, that 20% of all ADRs can be avoided.[250] Considering the many reasons causing an ADE, like prescription mistakes, wrong dispensations, contraindications with multi-morbid patients taking a variety of drugs, inadequate patient education etc., it becomes obvious that many ADE cases are not related to unknown or wrong dosage or similar causes.[251] In our example, the hypothetical death number would be reduced to 0.157.

Next, the number of years a child would have lived after avoidance of a death are estimated (average years lost per death). Assuming that the average age of such a child would be 9,

[250] Rottenkolber D, Schmiedl S, Rottenkolber M, et al. (2011) Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiol Drug Saf 2011;20:626–34.

[251] Cf. Smyth, RMD et al. (2012). Adverse drug reactions in children – A systematic review. PLOS One, 7/3, e24061

which is the average of 0 - 18 years, and that the average life expectancy at birth for a European citizen is 81 (2014),[252] we arrive at an estimate of the years of life gained of 72.

To attach an economic value to a statistical life (VSL) per year is an elusive exercise. As an average person contributes through taxes and other payments as much as it consumes in terms of uprising and education, security, traffic and public utility infrastructure usage, health and social care, social security and old-age receipts etc. One may conclude that contributions and consumptions are on average equal and hence that no value (VSL) should be attached from an economic point of view.

Nevertheless, various methods and values have been discussed in the literature,[253] and WHO guidelines suggest that countries should aim to spend between one and three times their Gross Domestic Product (GDP) per capita for one of their citizens per QALY gained from a health-related treatment. This puts the value of a life in Luxembourg between $111,162 – $333,486, the value in Mexico between $10,307 – $30,921 etc.[254] For our purposes, we use €50,000 as the value of a statistical life per year, because it is an "international standard most private and government-run health insurance plans worldwide use to determine whether to cover a new medical procedure."[255]

The value for avoidable mortalities is again assumed to be 20%.

Table 48 Summary of value for avoidable mortality variables used in the CBA model

Indicator name	Avoided mortalities
Variables	• Number of reported serious ADEs • Number of reported deaths from ADEs • Total mortalities from ADRs for the period • Avoidable mortalities as % of ADR cases • VSL (Value of a statistical life) per year • Average years lost per death
Formulae	(Number of reported deaths from ADR cases/Number of reported serious ADR cases (total mortalities from ADR) * number of paediatric cases) * Avoidable mortalities as % of ADR cases * VSL (Value of a statistical life) per year * Average years lost per death

[252] http://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics

[253] See Adlard, N., Kinghorn, P., & Frew, E. (2014). Is the UK NICE "Reference Case" influencing the practice of pediatric quality-adjusted life-year measurement within economic evaluations? Value in Health, 17(4), 454-461; Molinari, N. A. M., Ortega-Sanchez, I. R., Messonnier, M. L., Thompson, W. W., Wortley, P. M., Weintraub, E., & Bridges, C. B. (2007). The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine, 25(27), 5086-5096; Alex Mayyasi (2016). How Children Went from Worthless to Priceless. http://priceonomics.com/the-price-of-a-child/ and the literature mentioned in these references.

[254] Ashenfelter, O. (2006). Measuring the value of a statistical life: problems and prospects. The Economic Journal, 116(510), C10-C23

[255] https://en.wikipedia.org/wiki/Value_of_life

E.3.3 Benefits from hospitalisation avoided

To estimate the percentage of cases in need of hospitalisation, we used data from FDA paediatric reviews when available. For other medicines, we had to apply values derived from the literature for ADEs in general. Smyth et al. report that across the outpatient children population 97.1% of ADE did only require ambulatory treatment.[256] In line with this, we assert that only 3% of all cases required hospitalisation.

The mean length of stay in days is taken from data of HSCI which report a mean stay of 8.6 days for ADEs.[257] This is supported by Rottenkolber et al., who estimate the average inpatient length-of-stay due to ADRs to be 9.3 days.[258] It should be noted that looking at more recent data on e.g. the cost of a "Healthcare Resource Group (HRG)" event (or the cost of a "spell" – the "period from admission to discharge within a single provider") for various paediatric care categories in England, the mean length of stay is probably considerably lower, at least in some countries.[259]

Mean cost per bed day are set at around €576, based on WHO data (mean of 8 EU high and low income countries in WHO-report 2008, inflated to 2015 by the ECB (European Central Bank) inflation index for hospital care. Comparing this value with other data, it seems a reasonable estimate.[260]

Total hospitalisation costs are then calculated as 3% of all serious ADEs, each case requiring on average 9 days of hospitalisation at a daily cost of €576.

The value for avoidable hospitalisations is again set at 20%.

Table 49 Summary of avoidable hospitalisation variables used in the CBA model

Indicator name	Avoidable hospitalisation
Variables	• % of cases in need of hospitalisation • Mean length of stay in days • Mean cost per bed day • Hospitalisation costs • Avoidable hospitalisation (Rottenkolber et al. 2011 and estimates)
Formulae	Number of paediatric ADRs * % of cases requiring hospitalisation*mean length of stay in days*mean cost per bed day (hospitalisation costs)*% of avoidable hospitalisations
Example	Citing the narrative above, the 3% of all serious ADEs in need of hospitalisation, is multiplied by the number of ADR cases as calculated earlier. This is multiplied by the mean length of stay of an average of 9 days (as taken from data of the NHS England HSCI, supported by Rottenkolber et al. for Germany), and multiply that with a mean cost per bed day as set at €576. Avoidable hospitalisation cost is estimated at 20% of all hospitalisations.

[256] Smyth, RMD et al. (2012). Op. cit

[257] Health and Social Care Institute (HSCI).

[258] Rottenkolber et al., op. cit.

[259] See NHS reference costs 2013 to 2014 at: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014

[260] Department of Health UK (2014). National schedule of references costs 2012–13 for NHS trusts and NHS foundation trusts, London.

E.3.4 Benefits from other serious Adverse Drug Events avoided

To account for other serious adverse drug events avoidable like those resulting in life-threatening events, disability, or permanent damage we introduce a separate benefits category. As seen earlier for Montelukast (FDA note on "Case selection of Serious Pediatric Cases"), in some instances, where such events occurred, FDA reports specifically on such reports received. In the Montelukast instance, 140 "pediatric serious cases" are reported, of which 4 relate to death, and probably most – if not all – others to hospitalisation, for which we account in a separate category. But to also take into account the possibility of a certain number of other serious cases relating to life-threatening events, disability, or permanent damage, we assume that 5% of these "pediatric serious cases" may relate to this. 5% of 136 (140 minus 4 death reported) leads to around 7 of such other serious adverse drug events.

For all other medicinal products, where no extra paediatric serious cases are reported for death, inpatient hospitalisation, etc. we use the same percentage. We assume that this more than sufficiently accounts for the probability that such cases may occur.

In order to calculate the cost of such a case, we furthermore assume that it will result in a 20% reduction in quality of life (QoL) over the rest of life (for 72 years), or 20% per value of a statistical life year (0.2 x 72 x 50,000). Here we also calculate the benefit as 20 % of such cases avoided.

Table 50 Summary of avoided reduced quality of life variables used in the CBA model

Indicator name	Avoided reduced quality of life/other serious adverse drug events avoided
Variables	• Prevalence of other serious adverse drug experience • Prevalence of other serious adverse drug experience (absolute) • Reduced quality of life
Formulae	Number of paediatric ADRs * % of prevalence of other serious adverse drug experience * value of a statistical life per year * average years lost per death * reduced quality of life

E.3.5 Benefits from ambulatory services/outpatient treatment avoided

The percentage of cases treated in outpatient care facilities is calculated as the overall number of cases minus those accounted for by death and by hospitalisation. For the mean costs related to visits to primary care physicians, such as GPs, an average cost value of €50 is used.

In addition, we assert that a certain percentage of such cases will attend or require emergency room attendance. No data on this are available for different countries; therefore, we use our own estimate of 20% of such cases emerging.

For the mean cost of emergency room attendance a value of €400 is applied, based again on our own estimate. Again, benefits in terms of avoidable outpatient treatments is set at 20% of overall costs calculated for this category.

Table 51 Summary of avoided outpatient treatment variables used in the CBA model

Indicator name	Avoided outpatient treatment
Variables	• % of cases treated in outpatient care facilities • Mean costs related to visits to primary care physicians, such as GPs • Share of ADR cases requiring emergency room attendance • Mean costs of emergency room attendance • Outpatient treatment total • Avoidable outpatient treatment
Formulae	(number of paediatric ADRs*% of cases treated in outpatient care facilities*mean costs related to visits to primary care physicians, such as GPs)+(share of ADR cases requiring emergency room attendance*mean costs of emergency room attendance)*avoidable outpatient treatment

E.3.6 Benefits from informal care services avoided

To estimate the (social) costs of informal care services required for all more serious cases requiring hospitalisation, we assert that 90% of inpatient cases require also informal care services. Based on the estimate for hospital days mentioned above, it is assumed that in each such case on average 9 days are lost. As the € value of the informal carer gross salary per year we insert the average value for Germany, which is towards the higher end across the countries covered by the 8 medicines. The benefits are estimated as 20% saved from the cost of the total lost time by informal carers.

Table 52 Summary of avoided lost time by informal care giver variables used in the CBA model

Indicator name	Avoided lost time by informal carers
Variables	• % of inpatient cases requiring informal care • Average days lost • Informal carer gross salary per year • Total lost time
Formulae	(Number of paediatric ADRs * % of cases requiring hospitalisation*% of inpatient cases requiring informal care*average days lost*informal carer gross annual salary/12 months/ 19,24 average working days per month)*% of avoidable hospitalisations

E.3.7 Additional proxy benefit for better treatment per paediatric episode

The value for so called additional benefits per paediatric episodes serves as a proxy for missed benefits deriving potentially from better treatment but not captured by any of the other benefits variables included in the model. This value is by nature difficult to monetarise precisely and is prone to over- or underestimation.

Consequently, to account for any other benefits not covered by the benefit categories explored so far, we impute a value of €10 for each of the paediatric episodes.

Table 53 Summary of additional benefit per paediatric episode variables used in the CBA model

Indicator name	Additional benefit per paediatric episode
Variables	• proxy value for missed benefits from better treatment
Formulae	Number of paediatric episodes* proxy value for missed benefits from better treatment

E.4 Intermediary results from the exploratory cost-benefit assessment

E.4.1 Preliminary observations

The estimated overall socio-economic benefits thus comprise of:

- Economic/financial benefits in cash, i.e. those which indeed result in cash savings to be expected by the statutory health insurances and national/regional national health services across Europe, depending on the type of health system financing approach in the respective countries
- Intangible/societal benefits

These benefits are contrasted with the overall cash costs to national/regional healthcare systems respectively the public (statutory) health insurances, the monopoly rents accruing to the stakeholders benefitting from the 6-month SPC. These stakeholders are not only the marketing authorisation holders ("industry"), but also at least in some health systems also wholesalers, pharmacies and the government through levying sales taxes.

From these data, we calculate the respective benefit/cost ratios for the 6-month extension period.

This result is then simply extrapolated towards a ten-year period by multiplying the net benefits for these initial 6 months by 20, and setting it in relation to the overall costs (monopoly rent) calculated for the extra 6-month SPC. When estimating the cost to Third-Party Payers like health insurances, we have to deduct the co-payments charged to patients.

We abstain from discounting future benefits, because given the present capital market environment for more and more (public) debts virtually no interest is charged.[261]

E.4.2 Therapeutic characteristics of medicinal products covered by the detailed assessment

Seven of the eight medicinal products covered by the detailed analysis in WP 2, and the data of which are used in our benefit-cost assessment for detailed assessment are for treating a *chronic* disease. The other medicinal product for treating an *acute* disease. Altogether, the products have to be taken by the patients:

- Daily (six medicines)
- Once (at most twice within two days; one medicine for an acute disease)

[261] http://www.bbc.com/news/business-32284393: "Interest rates are now negative, below zero, for a growing number of borrowers, mainly in the financial markets. It means in effect they are being paid to borrow someone else's money."

- Once (1 medicine; the infusion may be administered again at a later date)

They cover a wide spectrum of *diseases*, whereby we mention here the main (adult) indication for the respective medicine:

- Asthma
- Cancer (breast cancer)
- Cardiology (high blood pressure; 2 medicines)
- Eye (Ocular hypertension and open-angle glaucoma)
- HIV
- Migraine
- Osteoporosis.

Of these 8 medicines,

- 5 are used *on-label* for certain age groups of children
- 3 are still used in children[262] although PIP result were negative.

In summary, these medicinal products cover a wide and diverse spectrum of medicinal products, which have successfully finalised a PIP.

E.4.3 Paediatric episodes and adverse events

This section presents a summary and detailed data on paediatric treatment episodes and estimates of related ADEs. All values are calculated for the 6-month SPC period. Mathematically, this leads to sometimes rather "uneven" numbers, whereas in reality, of course, all events come in discrete numbers.

Table 54 provides a summary overview of the percentage of all episodes, related to paediatric treatment interventions. For four of the drugs this value is below 1%, and for one of them even 0.09%. Remembering that for 3 medicines no on-label information has been forthcoming, this is not surprising. Only one drug has a very sizeable paediatric share of about 38% compared to the overall number of episodes, i.e. including treatment of adult patients.

Table 54 Percentage of all episodes related to paediatrics

% of episodes related to paediatrics	Absolute number of drugs	Individual % values
< 1%	4	0.09%; 0.21%; 0.33%; 0.83%
1% - < 5%	1	1.48%
5 - <10%	2	7.39%; 9.52%
10% +	1	37.6%

[262] ADE reports available for all drugs from both FDA and EMA for children and adults separately

Closely related to the above results is the absolute number of paediatric episodes we estimated for the 6-month period. For two medicines, this value is below 1,000, for three below 5,000. And only two achieve more than 100,000 – the highest value is 405,000. This last value refers to the medicine for an acute disease, Migraine. The other medicine of this group is for treating Asthma.

Table 55 Number of paediatric episodes (6 months)

Number of paediatric episodes	Number of drugs	Individual values
< 1,000	2	323; 770
1,000 - < 5,000	3	1,017; 3,209; 4,351
5,000 - <100,000	1	12,644
100,000 +	2	206,986; 405,096

Data on our estimate of serious paediatric ADE reports given as % of all paediatric episodes are reported in Table 56. Except for the Osteoporosis medicine with 0.39% and the HIV medicine with 0.41% of all episodes, the share for all other drugs is with below 0.04% (and as low as 0.0002%) relatively to quite low. To account for likely underreporting, we multiplied the number of ADEs entering our calculations by 2 (for death, which is regularly reported and to some extend even over-reported – FDA and EMA mention double reporting in several instances), and up to five for less serious events.

Table 56 Serious paediatric ADE reports as % of all paediatric episodes

Serious paediatric ADE reports as % of all paediatric episodes	Absolute number of drugs	Individual % values
< 0.010%	2	0.00021; 0.005%
0.010% - < 0.025%	2	0.016; 0.017%
0.025% - <0.05%	2	0.032%; 0.034%
0.05% +	2	0.394; 0.414%

From these percentages, the following numbers of serious paediatric ADEs per period (6 months) were estimated[263]. Only for the drug with the largest proportion of paediatric episodes, the Asthma medicine, this value is with 34 considerable. As already mentioned, in our later calculations we apply considerably higher values to take account of possible underreporting.

[263] As already mentioned, these figures are derived from mathematical computations and therefore are not reported in integers.

Table 57 Number of serious paediatric ADEs (6 months)

Number of serious paediatric ADEs	Number of drugs	Individual values
< 1	3	0.17; 0.25; 0.87
1 - < 5	4	1.27; 1.47; 2.00; 4.22
5 - < 25	0	
25 +	1	34.30

All of the above tables are derived from the detailed data as reported for each of the 8 medicines in the following overview table:

Table 58 Paediatric episodes and adverse events – detailed data for 8 medicines

Drug identification letter	**Explanatory note**	**Drug E**	**Drug H**	**Drug F**	**Drug A**	**Drug C**	**Drug B**	**Drug G**	**Drug I**
Indication / diagnosis; pharmaceutical dose form;		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of episodes related to paediatrics	EudraVigilance data mirror the actual distribution of therapeutic interventions across the population. The number of ADR reports for babies and children up to the age of 17 are calculated as share of all reports on originator medicine.	0.21%	0.33%	1.48%	37.59 %	9.52%	7.39%	0.83%	0.09%
Paediatric episodes		3,209	770	4,351	206,986	1,017	405,096	12,644	323

Drug identification letter	Explanatory note	Drug E	Drug H	Drug F	Drug A	Drug C	Drug B	Drug G	Drug I
Number of serious paediatric ADE reports as % of all paediatric episodes per period	Based on paediatric review reports by the FDA where available (for a given period). Complemented by estimates based on EudraVigilance data for a six-month period	0.005 %	0.032%	0.034%	0.017 %	0.414%	0.00021 %	0.016%	0.394%
Number of serious paediatric ADEs	No. of paediatric episodes x % of ADE episodes related to paediatrics x 0.01	0.17	0.25	1.47	34.30	4.22	0.87	2.00	1.27

E.4.4 Monopoly rents and net costs to health system payers

Next, we briefly summarise the data on monopoly rents and net costs to health system payers estimated as reported in Table 59 further below. Starting point are the pharmaceutical industry (marketing authorisation holders) monopoly rents as calculated in Chapter 3. As these data are based on wholesale prices, they do not reflect the true costs to health systems, respectively the national/regional payers and the statutory health insurances – depending on the national approach to financing of healthcare services.

Additional beneficiaries are pharma wholesalers, pharmacies as well the government (where VAT or sales tax is levied on medicinal products), all of which may also participate in this monopoly rent. Based on research by the German Ministry of Health, 2010[264] it is estimated that in Germany – the by far largest European market -, the monopoly rent to industry accounts for only 75.5% (industry revenue from wholesalers) of overall monopoly rent. 4.5% accrue to wholesalers, 4% to pharmacies, and 16% to the state from sales tax/VAT.

In some countries or regions, e.g. with NHS systems, no wholesalers may be involved, or in others no sales tax may be levied on medicines. To account for this, we assume that on average the monopoly rent to industry accounts for 87.5% of overall rent, i.e. 12.5% accrue to other beneficiaries (half of the percentage accruing to them in Germany). 12.5% of 87.5% are 14.3% - this is the percentage value by which the monopoly rent estimated in Chapter 3 was increased for our purposes.

[264] http://www.bundesgesundheitsministerium.de/fileadmin/redaktion/pdf_misc/Infografiken-Arzneimittelpreise.pdf Data are for March 2010.

To arrive at final overall costs to the "system", this sum needs to be reduced by an estimate of the (co-) payments charged to patients respectively their parents. A reasonable estimate of these co-payments from patients is almost impossible to make due to the very wide variation in the regulations in each of the countries concerned. Whereas e.g. in Germany no co-payments are required for paediatric prescriptions, in some countries a fixed amount of around or somewhat more than € 5 per prescription is mandatory. In others the co-payment is not fixed but depends on the overall annual burden from prescription medicines, and this may vary from patients who have to pay for the total price of the medicinal product to others with a heavy burden of medical expenses who have to pay only a small percentage or even nothing. Furthermore, the income situation of the family or the patient may also affect the co-payment amount.

To account for this reduction in costs accruing to the final payer,[265] we introduced the simple assumption that for each (adult and paediatric) treatment episode the Third-Party Payer receives a lump sum of €5. This allows us to arrive at a reasonable estimate for the overall net cost to the healthcare system as reported in the below table on *Monopoly rents and net costs to health system payers*.

As can be seen in Table 59, for these 8 medicines overall net extra cost for the 6-month extension is estimated at €551m to health systems, or more than half a billion Euros. Of the monopoly rent, €517 m accrue to industry, and €72.4 m to other stakeholders benefitting (wholesalers, pharmacies, states). The co-payments by patients of €38.5 m are not accounted for as extra costs, because we assume that they may have taken anyhow these or other medicines for which similar co-payments would have to be paid.

Note that this does not hold for one medicinal product – drug F. Due to the low price per treatment episode, the full cost of the monopoly rent is allocated solely to patients. Because of the low number of pills per episode (usually one – at most 2 over two days - for a child per treatment episode) and the low costs, our assumptions imply that Third-Party Payers do not encounter extra costs because the full costs are covered by patient payments, i.e. in this case patients will indeed pay fully for the extra monopoly rent. Of course, without the existence of the monopoly rent, their payments would be considerably lower during the 6-month period. Note that our assumptions cover, as an average, all countries where a product is marketed. For a single country, like in Germany, also for this drug the statutory health insurances would pay the extra cost rather than the patients, because for children no co-payments are due in Germany.

[265] Depending on the concrete situation of the specific medicinal product, the price per episode and the co-payment rules in the respective country, this argument may not hold, because without the extra SPC patients nevertheless would have to make co-payments of this – or a somewhat lower - amount. If this holds, the extra cash costs to health systems would be up to about 10% more in the given scenario than reported in the table, and equal to "Total monopoly rent".

Table 59 Monopoly rents and net costs to health system payers

Drug identification letter	Explanatory note	Drug E	Drug H	Drug F	Drug A	Drug C	Drug B	Drug G	Drug I	Sum
Total benefits paediatrics (I + II + III + IV + V + VI)		44,448€	25,880€	150,420€	4,938,687€	316,847€	4,113,994€	271,897€	95,591€	9,957,764€
Cash cost - industry monopoly rent - of SPC extension	Wholesale based industry revenue	146,496,778€	31,183,348€	105,217,160€	58,121,640€	9,355,013€	14,105,120€	113,220,733€	39,548,178€	517,247,970€
Cost - other stakeholders' monopoly rent - of SPC extension	Revenue accruing to wholesalers, pharmacies, government(s) (VATax) - at an average 14% on industry revenue	20,509,549€	4,365,669€	14,730,402€	8,137,030€	1,309,702€	1,974,717€	15,850,903€	5,536,745€	72,414,716€
Total monopoly rent	Total monopoly rent to all stakeholders	167,006,327€	35,549,017€	119,947,562€	66,258,670€	10,664,715€	16,079,837€	129,071,636€	45,084,923€	589,662,686 €
Minus revenue from co-payments of patients	Revenue to health systems from co-payments of patients; Assumption of € 5 per episode, varies greatly across countries	7,529,141€	1,171,257€	1,469,912€	2,753,208€	53,440€	16,079,837€	7,616,872€	1,832,860€	38,506,528€
Net cash cost to healthcare system (statutory insurances or NHS)		159,477,186€	34,377,760€	118,477,650€	63,505,461€	10,611,275€	0	121,454,764€	43,252,063€	551,156,158€

E.4.5 Cash benefits and financial return to health system payers

Table 60 summarises the estimates relating to the potential avoidance of ADRs and the cash savings resulting there from for health system payers. This concerns hospital stay and outpatient encounters (emergency room visits and ambulatory services) avoided, all of which would have direct cost implications.[266] Except in the case of the Migraine medicine, the resulting values are negligible, particularly in view of the monopoly rents reported above, and the results would remain negligible even if we increased the number of ADEs included in the calculations by 10 (or even more). Such a figure would imply that only 2 in 100 ADEs are reported on average, i.e. a rate of underreporting of 50. For the migraine product no benefit-cost ratio is given, because all monopoly rent cost accrue to patients.

Table 60 Cash benefits and financial return to health system payers

Drug identification letter	**Drug E**	**Drug H**	**Drug F**	**Drug A**	**Drug C**	**Drug B**	**Drug G**	**Drug I**	**Sum**
Cash benefits (avoidable hospital and out-patient [ambulatory] costs)	97 €	148 €	870 €	31,000 €	2,495 €	513 €	1,183 €	751 €	37,056 €
Financial (cash) benefit-cost ratio for a 6-month period	0.000	0.000	0.000	0.000	0.000	-	0.000	0.000	0.000
Cumulative financial (cash) benefit-cost ratio after 10 years	0.000	0.000	0.000	0.010	0.005	-	0.000	0.000	0.001

The implications of these estimates and calculations are that, based on the assumptions made and the exploratory calculations undertaken, the cash costs of more than half a billion Euro are not to any noticeable extent compensated for by equivalent cash savings. This holds for all medicinal products covered by our analysis. Whereas we estimated more than half a billion Euro in monopoly income to various stakeholders, the estimated cash savings are with €37,000 for the 6-month period, or €741,000 for a ten-year period, negligible. The reasons for this are twofold: the very low use of most products for paediatric populations – with the exception of drug D (and drugs E and F to a lesser extent), and the usually very low number of ADEs. Even after 10 years, the estimated cumulative financial benefit-cost ratio across all 8 drugs is with 0.00134 virtually zero. This translates into a financial rate of return of almost minus 100%.[267]

[266] Note that this assumption implies that marginal cost is equal to average cost. In a fee-for-service system this will hold, whereas in a national or regional public health service system this may not be the case.

[267] In financial or capital markets, this would imply total loss of investment.

E.4.6 Intangible benefits and societal return

When taking non-cash (intangible) benefits into consideration, the picture changes somewhat. Here we subsume benefits expected from improved actual treatment of children, which result in:

- Reduced mortality
- Improved quality of life (QoL) experiences due to long-term disabilities
- Time saved by informal carers

Furthermore, in order to account for further benefits not accounted anywhere else we add a hypothetical benefit of € 10 per treatment episode.

The results are presented in the following table:

Table 61 Intangible benefits and societal return

Drug identification letter	**Drug E**	**Drug H**	**Drug F**	**Drug A**	**Drug C**	**Drug B**	**Drug G**	**Drug I**	**Sum**
Non-cash (intangible) benefits (avoidable mortality and disabilities, improved QoL, informal carers costs avoided, plus additional benefits per episode) (I + IV + V + VI)	44,351 €	25,732 €	149,550 €	4,907,688 €	314,352 €	4,113,481 €	270,714 €	94,839 €	9,920,707 €
Intangible (non-cash) benefit-cost ratio for a 6-month period	0.000	0.001	0.001	0.077	0.030	-	0.002	0.002	0.018
Cumulative intangible benefit-cost ratio after 10 years	0.006	0.015	0.025	1.546	0.592	-	0.045	0.044	0.360

For four medicinal products with very few paediatric treatment episodes compared to all treatment episodes (the values are 0.21% for drug E, 0.33% for drug H, 1.5% for drug F and 0.09% for drug I), the benefits estimated are also here very marginal with less than € 100,00 for the 6-month period. Also the 6-month and 10-year benefit-cost ratios are very marginal to negligible. A ratio value of 1,000 would signal a rate of return of 0.00%, i.e. they all have very high negative rates of return for this short period.

For the product with the largest share of paediatric treatment episodes – drug A with 38% - the situation is very different. This asthma drug has an estimated intangible benefit/cash cost ratio of 0.077 for 6 months. For ten years, we obtain a benefit/cost ratio of 1.546, or a positive rate of return of 55%.

The next highest values are estimated for drug C, the HIV medicine. Its comparable values are 9.5% for the share of paediatric treatment episodes, 0.030 for the 6-month benefit-cost ratio, and for the 10-year period a ratio of 0.592 or a negative rate of return of 41% is estimated.

Aggregating the data for the seven medicinal products included into the above benefit-cost calculations, an overall 6-month benefit-cost ratio of 0.018 is estimated, and for the 10 year period a ratio of 0.36 or a negative rate of return of 64%. In other words, whereas the extra

cost due to the monopoly rent are estimated at more than half a billion Euro, the overall intangible benefits estimated sum up to almost € 200m after 10 years.

Looking also at the Migraine drug B, for which no extra costs to the health system arose, we can nevertheless compare the estimated overall monopoly rent of €16m with the estimated non-cash benefits. For the six-month period, we estimate intangible benefits of around €4m, which implies that already after two years a hypothetical break-even point would be reached. Over a 10-year period very substantial benefits of around €80m would accumulate, implying a hypothetical benefit-cost ratio of 5 ((€4 [for 6 months] x 20 [six months periods])/€16), or a rate of return of 400%. Adding these €80m to the €191m estimated for the seven other products, overall benefits of €199m for 10 years are estimated, to be contrasted with costs of more than half a billion Euros.

E.5 Summary data and results of the exploratory cost-benefit assessment

E.5.1 Estimating the overall benefit/cost ratio per medicinal product

Adding up cash and non-cash benefits as estimated above, and setting them into a ratio to the estimated net cash cost resulting from the monopoly rent for the extra 6-month SPCs to health systems, the following values are obtained:

Table 62 Overall benefit/cost ratio per medicinal product

Drug identification letter	**Drug E**	**Drug H**	**Drug F**	**Drug A**	**Drug C**	**Drug B**	**Drug G**	**Drug I**	**All drugs**
Non-cash (intangible) benefits (avoidable mortality, reduced QoL, informal carers costs + add. benefits per episode) (I + IV + V + VI)	44,448 €	25,880 €	150,420 €	4,938,688€	316,847 €	4,113,994 €	271,897 €	95,590 €	9,957,763€
Total socio-economic benefit-cost ratio for a 6-month period	0.000	0.00075	0.001	0.078	0.030	0.000	0.002	0.002	0.018
Total cumulative benefit-cost ratio for 1 0 years	0.006	0.01506	0.025	1.555	0.597	0.000	0.045	0.044	0.361

The highest value for the 6-month period is estimated for drug A with 0.078, followed by an already very low value of 0.016 for drug C. It may be remembered that for drug A about 38% of all treatment episodes relate to paediatric use, and that drug C boosts the next highest value with almost 10%. For the five other medicines, the overall benefit-cost ratio is negligible and more or less zero.

When calculating the same values for a ten-year period, drug A is the only drug which achieves a positive benefit-cost ratio of 1.555 or 55.5% rate of societal return. Next in line is drug C with 0.31 or minus 69%. All other drugs show also for this long-term value negligible results. Taking also into account drug B – a drug for which we did not estimate extra monopoly cost to health systems because all extra costs are covered by patients' co-payments – then this would achieve the by far highest rate of return of more than 400% (as mentioned above in section 4.3.6).

Extrapolating the cumulative result across the seven drugs over twenty 6-month periods or 10 years in a linear fashion without discounting delivers an overall cumulative benefit-cost ratio of only 0.35 or about minus 65%. Depending on expectations about the future, this result may change considerably:

- If discounting is introduced, i.e. in case during coming years interest rates for public organisations will rise again above 1% or 2%, this rate will decrease considerably, because all costs are experienced "now", whereas estimated benefits will accumulate only over an extended period of unknown length.
- If we assume that over time new treatment regimens are introduced, new drugs enter the market, etc., then benefits will decrease to some or even a greater extent, and again the benefit-cost ratio will decrease even further.
- On the other hand, in case it is assumed that the knowledge about the new insights gained from the PIPs and on-label use will diffuse more widely and lead to a further increase in on-label use for some of the medicines, then the benefit-cost ratio may even somewhat increase with time.

E.5.2 Comprehensive, detailed data per medicinal product

A comprehensive overview of the results of the exploratory benefit-cost assessment performed, based on the data, estimates and assumptions detailed above is available in the Confidential annex. More details on each of the medicinal products are provided in a separate data sheet for each in this report.

E.6 Sensitivity analyses

Based on the initial exploratory cost-benefit assessment, we undertook a comprehensive sensitivity analysis, which included the following steps:

E.6.1 Partial sensitivity analysis

On the variables judged on the one hand most uncertain and, on the other hand, most relevant for the results of the benefit/cost analysis, a partial sensitivity analysis was performed. We thus identify the most sensitive and uncertain ones in terms of data

availability and robustness of underlying assumptions and estimates. In a Monte Carlo sensitivity analysis, the identified most sensitive variables are subsequently varied together, but independently of each other, in order to test the robustness of the overall results.

In the following table the list of variables examined is depicted, including the reasoning for their selection and our assessment of their uncertainty. :

Table 63 Variables selected for partial sensitivity analysis

Variable	**Selection criteria for partial sensitivity analysis**
Number of paediatric episodes (+100% and – 50%)	This is used as a proxy variable, because it will lead to a doubling (respectively cutting by half) of all estimates for ADEs and the benefits calculated for the reduced incidence of such events. A major uncertainty in the data stems, on the one hand, from the fact that ADE reporting itself is only a next best approximation to the number of paediatric ADRs, which implies an overestimation of the real number of adverse reactions; and on the other hand, from the assumed underreporting of ADEs. It should be remembered that, in order to be on the save side, we increased the estimates for death by 100% already in the earlier estimates, and those for other adverse events up to 400% or five-fold.%.
VSL (Value of a statistical life) per year (+100%)	Economically valuing life in monetary terms is a difficult undertaking. As there is no standard concept for the financial value of a specific human life, any estimate is highly sensitive to preferences and perspectives. To take care of this uncertainty, we also calculate with the VSL doubled.
Avoidable hospitalisation (+ or - 50%)	This data relates to Rottenkolber D. et al (2011), but is also based on own estimates and is inherently difficult to assess in the absence of actual data, given also the probable variation across disease domains and medications. We varied this variable by +/- 50%
Avoidable outpatient treatment (+or - 50%)	Same as above.
Prevalence of other serious adverse drug events (+100% or – 50%)	No data exists on the prevalence of other serious consequences of ADRs such as permanent disabilities or chronic diseases, and the consequent change in quality of life. Any estimates, similar to studies in general on ADE and ADR incidence rates must be viewed with circumspection. To account for the inherent uncertainty, we increase the number of such events by 100% and also decreased it by 50%.
Additional benefit in € per paediatric episode (+ 100% or another € 10 versus a decrease by 50% to € 5)	The value for what we called additional benefits per paediatric episode serves as a proxy for missed benefits deriving potentially from better treatment but not captured by any of the other benefit variables included in the model. This value is by nature very difficult to monetarise precisely and is prone to over- or underestimation. We undertook calculations based on variation of +100% or a value of € 20 versus a decrease by 50% to € 5.

E.6.2 Number of paediatric episodes and ADEs (+ 100% versus – 50%)

Doubling of the number of paediatric episodes leads, of course, also to a doubling of the estimated absolute number of ADEs by +100%, and thereby to a doubling of all benefit categories estimated, and of all benefit-cost ratios.

Reducing the estimates of paediatric episodes by 50%, i.e. cutting them by half, will similarly half all benefit and ratio estimates.

The same holds for doubling or cutting by half the estimates of ADEs without changing the estimates for paediatric episodes.

When considering this, it may be remembered that the estimates for the overall percentage of all treatment episodes arising in the paediatric context are probably quite valid as demonstrated by comparing USA and European data. The same would apply to the absolute number of paediatric episodes, which are based on reliable market data.

E.6.3 Value of a Statistical Life (VSL) per year (+100%)

The variation by +100% shows that on average we can observe an improvement in the benefit-cost ratios by 67%, with considerable variation across medicines. As death is not a major factor here, this is almost exclusively due to its indirect impact on the benefits estimated for a reduction in other serious consequences of ADRs such as permanent disabilities or chronic diseases, leading to a reduced quality of life (QoL).

Table 64 Sensitivity of variable 'value of a statistical life'

Variable: Value of a statistical life	**Estimated change: +100 % from initial calculation**							
Drugs	E	H	F	A	C	B	G	I
Total cumulative benefit-cost ratio after 10 years – Initial calculation	0.006	0.015	0.025	1.555	0.597	n.a.	0.045	0.044
Benefit-cost ratio – + 100% of events	0.007	0.026	0.043	2.447	1.169	n.a.	0.068	0.086
Change of ratio in %	27.5%	69.6%	70.4%	57.3%	95.8%	n.a.	53.0%	95.7%

For drugs C and I the impact is most pronounced. The number of overall paediatric episodes estimated for them is very low, and cash items are negligible. The only relevant benefit item is the indirect impact of the increased value used for VSL on the benefit estimates resulting from the assumed reduction of other very serious drug reactions (reduced QoL).

The opposite holds for drug E, here the impact of a doubled value for VSL is very small. This is due to the relatively very low number of ADEs. It follows that almost all benefits result from the assumed lump sum benefits allocated to each paediatric episode resulting from better treatment options (a value of €5 was asserted) plus avoided other "significant" ADEs (here also a value of € 5 was estimated).

E.6.4 Avoidable hospitalisations (+/-50%)

The calculations with an increase of this variable by 50%, as well as a decrease, show no noticeable change in overall benefit-cost ratios (less than 1% change observed).

E.6.5 Avoidable outpatient treatments (+/-50%)

The calculations with an increase of this variable by 50%, as well as a decrease, show no noticeable change in the overall benefit-cost ratios (less than 1% change observed).

We did not include the number of deaths related to paediatric episodes into our sensitivity estimates as a separate variable, because such events were reported for only one of the eight medicinal products. And even for this drug a further doubling (we already increased it by 100% to account for potential underreporting) of the absolute numbers would increase the benefits and rations only by about 7%.

E.6.6 Prevalence of other serious adverse drug events (+100% or minus 50%)

This factor accounts for the possibility that up to 5% of all very serious ADEs estimated may result in a rather serious life-long adverse reaction leading to a 20% decrease in QoL over the rest of the life of the child, based on 72 extra years.

The variation by +100% causes on average an increase in estimated benefits by 66%. The reduction by 50% leads to an average decrease of minus 33%

Table 65 Sensitivity of variable 'prevalence of other serious adverse drug events'

Variable: Prevalence of other serious adverse drug events	**Estimated change: +100 % or minus 50% from initial calculation for 10 years**							
Drugs	E	H	F	A	C	B	G	I
Total cumulative benefit-cost ratio after 10 years – Initial calculation	0.006	0.015	0.025	1.555	0.597	n.a.	0.045	0.044
Benefit-cost ratio – + 100% of events	0.007	0.026	0.043	2.333	1.169	n.a.	0.068	0.086
Change of ratio in %	27.5%	69.6%	70.4%	50.0%	95.8%	n.a.	53.0%	95.7%
Benefit-cost ratio – minus 50% of events	0.005	0.010	0.016	1.167	0.311	n.a.	0.033	0.023

Variable: Prevalence of other serious adverse drug events	Estimated change: +100 % or minus 50% from initial calculation for 10 years							
Change of ratio in %	-13.8%	-34.8%	-35.2%	-25.0%	-47.9%	n.a.	-26.5%	-47.8%

Earlier, when exploring a 100% increase in the VSL, we noted that "for drugs C and I the impact is most pronounced. The number of overall paediatric episodes estimated for them is very low, and cash items are negligible. The only relevant benefit item is the indirect impact of the increased value used for VSL on the benefit estimates resulting from the assumed reduction of other very serious drug reactions (reduced QoL)." As the benefits due to the avoidance of other serious adverse drug events are directly connected to the VSL, it is not surprising that the relative impact on benefit-cost ratios is very similar.

E.6.7 Additional benefit in monetary value per paediatric episodes (+100% or – 50%)

The increase by +100% to € 20 shows that, on average, we can observe an improvement in the benefit-coast ratios by 32%. Whereas for drug A the value almost doubles with 72%, i.e. almost all benefits are derived from this variable, the increase with slightly more than 3% is very small for drugs E and H. For both of them the values estimated for serious paediatric ADEs as % of all paediatric episodes per period are the highest of all medicines, which implies that here the comparably highest benefits are derived from avoidance of ADRs and not from this variable.

Cutting the estimated benefit amount by half to only € 5 gives a reduction by minus 16% on average, with considerable variations across drugs (from minus 1.6% to minus 36%).

Table 66 Sensitivity of variable 'prevalence of other serious adverse drug experiences'

Variable: Prevalence of other serious adverse drug experiences	Estimated change: +100 % from initial calculation							
Drugs	E	H	F	A	C	B	G	I
Benefit-cost ratio – Initial calculation (10 €)	0.006	0.015	0.025	1.555	0.597	n.a.	0.045	0.044
Benefit-cost ratio – + 100% (to 20 €)	0.010	0.020	0.033	2.207	0.616	n.a.	0.066	0.046
Change in %	72.2%	29.7%	28.9%	41.9%	3.2%	n.a.	46.5%	3.4%
Benefit-cost ratio – minus 50% (to 5 €)	0.004	0.013	0.022	1.229	0.588	n.a.	0.034	0.043

Change in %	-36.1%	-14.9%	-14.5%	-21.0%	-1.6%	n.a.	-23.3%	-1.7%

Reviewing these results, four major variables were selected for the next step, the Monte Carlo analysis:

- Number of paediatric episodes
- VSL (Value of a statistical life) per year
- Prevalence of other serious adverse drug experience impacting on QoL
- Additional benefit in € per paediatric episode

E.7 Monte Carlo sensitivity analysis

This analysis is based on a random sampling process, which approximates the expected values for the benefit/cost ratios and their variance. The input variables are permitted to vary within defined symmetric (plus and minus) boundaries at random, and it is assumed that their probabilities are not interdependent. We assume a discrete uniform distribution, i.e. a symmetric probability distribution whereby a finite number of values (here in steps of ten or more) are equally likely to be observed; every one of n values has equal probability 1/n. A Monte-Carlo analysis allows us to obtain an initial indication of the likely uncertainty range of the overall assessed value, the benefit/cost ratio, and the implied time period when for a specific drug the societal break-even point may be reached.

Based on the above identified most sensitive and uncertain parameters and the results obtained via the partial sensitivity analyses, we selected variables and these uncertainty boundaries for undertaking the Monte-Carlo analysis, see the table below.

Table 67 Selected variable for Monte-Carlo analysis

Variable	**Range of variable value applied to Monte Carlo simulation**
Number of paediatric episodes (+50% and – 50%)	The respective value is varied across a range between (0.5 x initial value) and (1.5 x initial value)
VSL (Value of a statistical life) per year (+50% and -50%)	Variation between € 25,000 and € 75,000
Prevalence of other serious adverse drug events (+50% and – 50%)	The respective percentage value is varied across a range between (0.5 x initial value) and (1.5 x initial value)
Additional benefit in € per paediatric episode (+50% and -50%)	Variation between € 5 and € 15

When varying all these variables simultaneously in one simulation (contrasted with only one variable per simulation in the partial sensitivity analysis) and using 1,000 iterations, we

receive a more complete picture of the margins of our estimates. To this end, the 5%, 50% and 95% quintiles are used to derive the worst, typical and best case scenarios.

The Monte Carlo sensitivity analysis was performed for three typical drugs of our sample of eight. The selection criteria are meant to match three different profiles in terms of their application (chronic or acute disease domain) and rate of ADE episodes in the paediatric population.

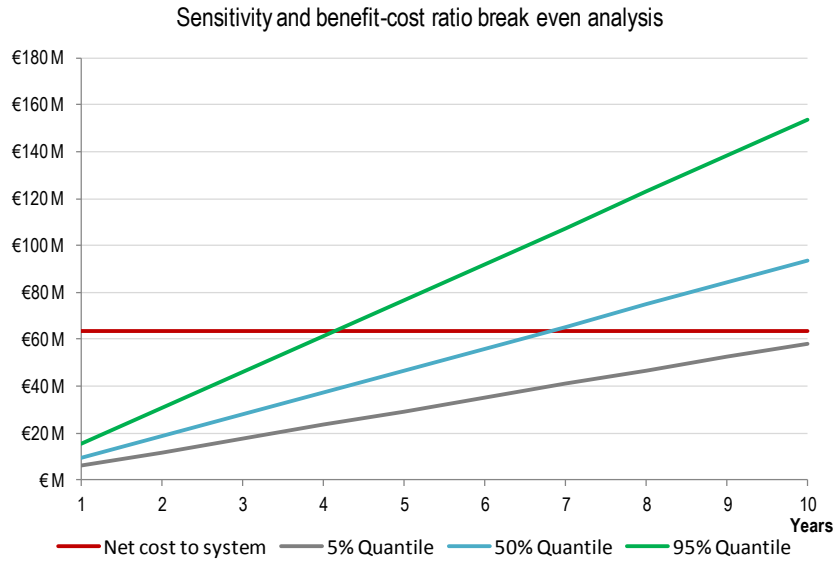
- Drug [redacted] is prescribed for a chronic respiratory disease and has a relatively high share of episodes relating to paediatrics
- Drug [redacted] is prescribed for treatment of HIV infections and has a comparatively medium share of episodes relating to paediatrics
- Drug [redacted] is a chronic disease drug for treating high blood pressure and has a comparatively low to very low share of episodes relating to paediatrics

E.7.1 Monte-Carlo simulation for drug A

The simulation for drug A shows that an average overall societal benefit is expected of close to €4.7m in the 6 months of the extension period. The cumulative benefits in the typical case would reach the break even point seven years after the SPC extension was granted.

For the 95% quintile, the Monte Carlo analysis delivers an estimate of € 7.7 m, which would allow reaching the break-even point already in year 4. On the other hand, looking at the other end for the 5% quintile, the break-even point would be obtained only after eleven years. Such a spread of 7 years (11 minus 4) is quite considerable, underlining the experimental character of our exploratory assessment.

Figure 45 Sensitivity test results for Drug A



Quintile	**Total societal benefits (6 months)**	**6-month benefit-cost ratio**	**Break even**

5% quintile	2,912,994 €	0.046	Year 11
50% quintile	4,667,788 €	0.074	Year 7
95% quintile	7,673,738 €	0.121	Year 4

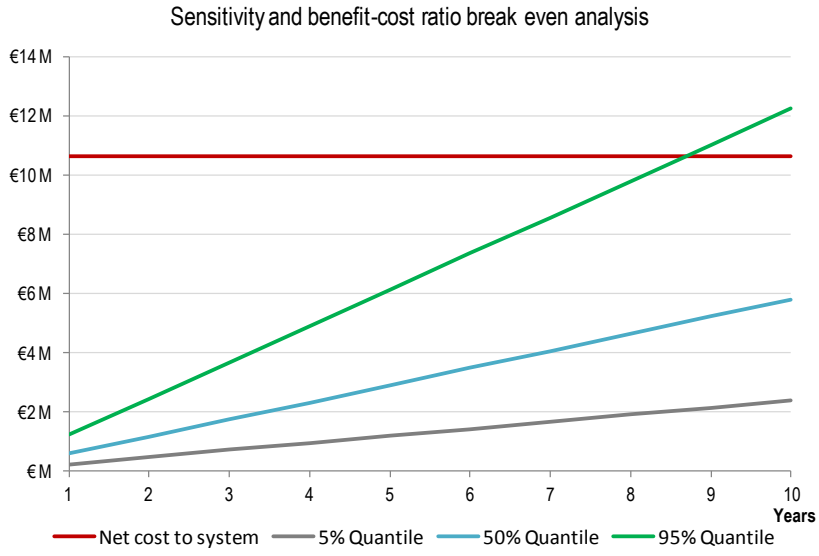
For drug F, it was estimated that the full cost of monopoly rent would be covered by co-payments of patients. If this were not the case, and the full cost of around €16m would have to be covered by the health systems, the 50% quintile value were the breakeven would be reached is 2 years – based on overall benefits of €4m for the 6-month period, and the spread would be about 1 year for the optimistic estimate (5% quintile), and close to 3 for the pessimistic estimate (95% quintile).

E.7.2 Monte-Carlo simulation for drug C

The simulation for drug C shows that an average overall societal benefit is expected of almost €290,000 in the 6 months of the extension period. The cumulative benefits would reach the breakeven point only 18 years after the 6-month SPC extension was granted.

For the 95% quintile, the Monte Carlo analysis delivers an estimate of € 663,000, which would allow reaching the break-even point already in year 8. On the other hand, looking at the other end for the 5% quintile, the break-even point would be obtained only after 43 years.

Figure 46 Sensitivity test results for Drug C

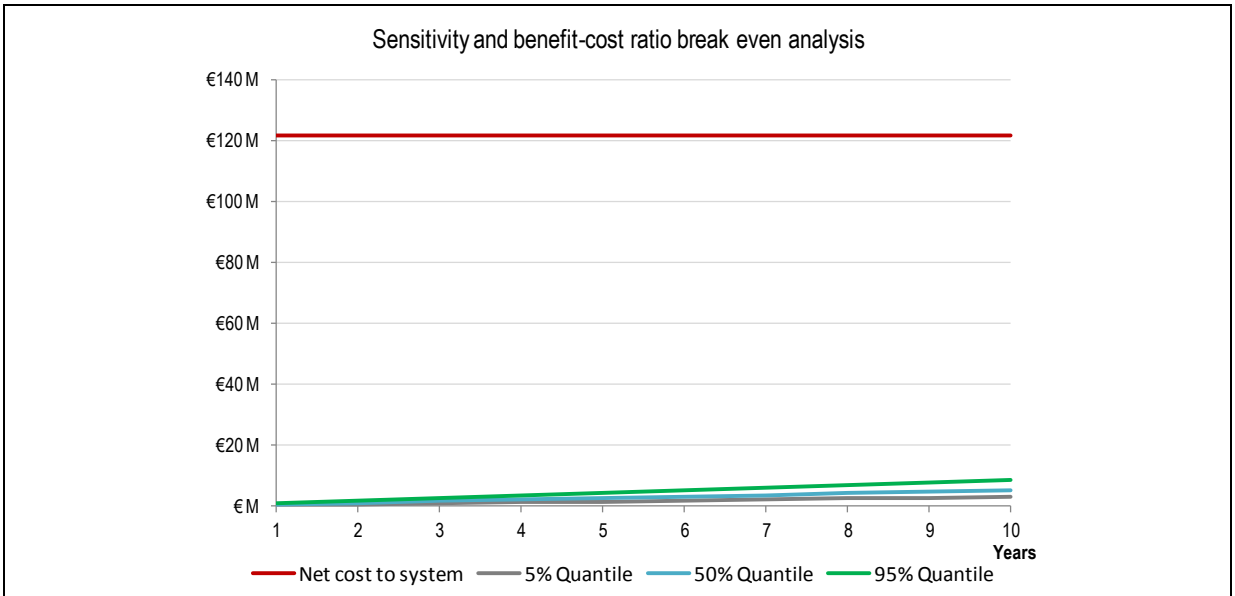


Quantile	**Total societal benefits (6 months)**	**Benefit-cost ratio**	**Break even**
5% quintile	122,477 €	0.012	Year 43
50% quintile	287,797 €	0.027	Year 18
95% quintile	663,271 €	0.063	Year 8

E.7.3 Monte-Carlo simulation for drug G

The simulation for drug G, which can be regarded as exemplary also for the remaining 4 drugs for which even lower benefit-cost rations were estimated earlier, shows minute benefits in comparison to the costs for the health system payers. Even in the optimistic scenario, a break-even point would be reached only after about 140 years, and for the 50% quintile we obtained a value of 234 years, for the 5% quintile of 407 years.

Figure 47 Sensitivity test results for Drug G



Quantile	**Total benefits paediatrics**	**Benefit-cost ratio**	**Break even**
5% quantile	149,248 €	0.001	Year 407
50% quantile	259,221 €	0.002	Year 234
95% quantile	432,383 €	0.004	Year 140

In summary, when considering the results for all eight drugs, the Monte Carlo simulation delivers quite interesting results: When considering a considerable variability in the four major drivers of benefits by plus and minus 50% in our estimates,

1. For the optimistic[268] estimates (95% quintile), one medicine will reach its break-even point already after 1 year, one after 4 and a third one after 8 years; five drugs will take 140 or more years even in this scenario
2. For the average scenario, the periods are 2, 7 and 18 years, and more than 230 for the other 5 drugs

[268] This implies, e.g., higher numbers of ADRs.

3. For the low estimates (5% quintile), the estimated number of years is 3, 11, 43 years and more than 400.

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